Volume 13, Number 3
MARCH 1953

Postgraduate Medicine

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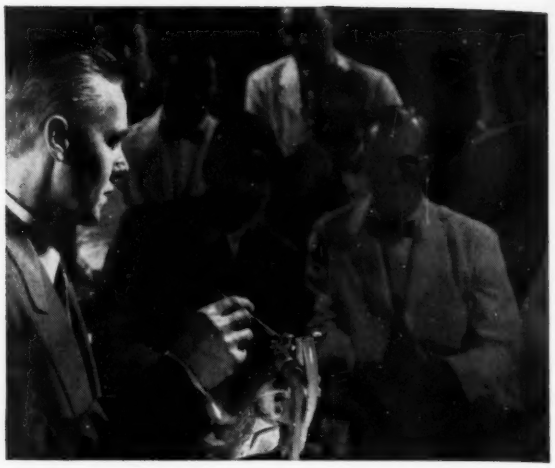

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1. Moses, C. and Peters, J.: Pennsylvania Med. J., *55*:1020, (Oct.) 1952.

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MARCH · 1953

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THE 1953 Assembly *OF THE*

INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

of North America

THE PALMER HOUSE, CHICAGO

November 2 to 5 (inclusive), 1953

The Influence of Drugs on Blood and Bone Marrow

FRANK J. HECK*

Mayo Clinic, Rochester, Minnesota

In the introduction of new drugs, one must consider critically their possible harmful effects on the blood and bone marrow. When there is a choice among several drugs, all of which have the same therapeutic effect but one of which occasionally harms a patient, use of the harmful drug should be excluded.

F. J. HECK

CHEMICAL investigation over the past 75 years has been responsible for the introduction of many drugs of great therapeutic value. While the pattern of response to a given drug is usually reasonably uniform, it has always been found that certain individuals react abnormally either with hypersensitivity or, what is less important, with hyposensitivity. As physicians we have recognized for many years the toxic effects of certain agents that have been used therapeutically because they would produce a result for which we were striving. Benzene, in spite of its recognized hazards, was used in the treatment of leukemia at a time when other methods of treatment were not available. The risks of such treatment had to be, and were, accepted. As newer methods of treatment with less toxic effects were developed, the older drugs were as a rule superseded, although in some instances certain drugs such as Fowler's solution for chronic myelogenous leukemia, after a period of disuse, again found favor because their sphere of activity had been restudied and certain definite advantages could be shown for them.

We have not always been quick to recognize the toxic reaction of drugs; it has sometimes required the description of a new clinical syndrome, the search for a possible etiologic agent and finally the recognition of the causative agent before we could clearly see the whole picture. This is best illustrated by the granulocytopenia which may be produced in sensitive individuals by aminopyrine. This excellent analgesic drug was synthesized in 1889 and introduced to medical practice shortly afterward. In 1922 Schultz[1] called attention to cases of a disease now known as "acute granulocytopenia," although in the first decades of this century there were individual case reports of similar type. In the years after 1922 there were many reports of cases of this type. Kracke[2] in 1932 reported his experimental attempts to reproduce the disease, since he was convinced that benzene ring derivatives played a role, but it remained for Madison and Squier[3] to demonstrate the role played by aminopyrine in the disease. So here we had a period of 45 years from the time of synthesis to the time of demonstra-

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

tion of the serious toxic effects in sensitive individuals.

It is difficult to estimate the proportion of people that might be affected by such a drug but certainly it is extremely low. For this reason ordinary clinical trials of drugs with reports as to lack of harmful effect on the blood must be believed with extreme caution. Most clinical trials involve only a hundred or a few hundred patients, whereas to demonstrate sensitivity, experience with thousands of cases is required. It therefore seems particularly appropriate at this time to again call the attention of the medical profession to the various types of reactions which may be brought about in the blood, especially now when so many new therapeutic agents are being introduced and when some of the older drugs known to produce such changes as granulocytopenia are again being recommended either in their original form or as chemical modifications with the hope that the toxic effect may be eliminated. Within the past few months combinations of aminopyrine with other drugs have been reported on in the literature, and recently a question has been raised as to why aminopyrine should not be used more extensively when given under careful supervision.

This brings us to a consideration of what should guide us in the selection of a drug. It seems reasonable that if there are several drugs with basically the same therapeutic action, if one of them shows definite toxic properties, then that drug should be eliminated from consideration. Only when the possible benefit from such drugs is balanced against the risk is one justified in using such preparations. Almost every day the physician makes use of drugs or procedures of this type and both physician and patient accept the "calculated risk" involved.

Reactions of the blood and bone marrow to drugs fall into a number of well recognized groups. In some of these a single element alone is affected while in others all bone marrow elements are involved, and in still others various combinations of cells are included leaving some cell lines intact. The clinical response to these effects is varied. At times there is a sharp, acute response during the time the patient is taking a drug with precipitation of symptoms that leave no question as to something being wrong. At the other extreme are the cases in which at first the symptoms are very vague and their onset is quite distant from the period in which medication is administered. There are no warning signs here that something is going amiss and the physician is allowed no latitude in withdrawing the drug, the effect on the blood and bone marrow being established some time after recovery from the illness for which the patient was treated; by this time, as we shall see a little later, irreversible and possibly fatal damage to tissues has already occurred.

Granulocytopenia

Probably the best recognized and most widely publicized group of cases in which there is a drug effect is that group best known under the name "granulocytopenia," originally introduced as "agranulocytosis" but also known by other names such as "malignant neutropenia." Since a number of conditions associated with leukopenia and neutropenia have no relationship to the condition under discussion, I should first define what I mean by granulocytopenia. From the original descriptions of Schultz, and a host of others, included primarily are those cases in which there is acute onset of an illness with chill, fever, commonly sore throat, aching of the bones, and a progressive decrease in the total leukocyte count and simultaneous decrease or disappearance of the neutrophils. The majority of the cases originally described were in women.

In the various reported series of cases of granulocytopenia, the mortality rate ran from 60 to 90 per cent. Ulceration of mucous membranes and less frequently of the skin was of common occurrence. The ulcers were usually flat and shallow and there was complete absence of any reaction about their edges, the lack of reaction being due to the absence of neutrophils. The course was commonly that of a septic infection, and bacteremia developed in some individuals. Necrosis of tissue, such as gangrene of the lung, was not infre-

quent in those patients who succumbed.

Many of the patients who died of granulocytopenia experienced a progressive reduction of leukocytes to levels of 200 to 400 per cubic millimeter of blood so that the lymphocytic line might also be involved, but it was very uncommon to see involvement of the erythrocytic or thrombocytic lines. In those patients who were going to recover, after a varying number of days in which there was a low count or complete absence of neutrophils, one would begin to find extremely toxic immature myeloid cells in the peripheral blood and, following this, the more mature cells which gradually lost their toxic appearance as the patient went on to recovery. In the recovery phase, too, leukocytosis might develop but this soon disappeared. If there was a repetition of the event, the clinical course and laboratory findings were essentially identical with those of the original attack. The bone marrow picture, if followed serially, depended on the severity of the process. One might find almost complete absence of myeloid cells except for a few blast forms, or one might, in less severe cases, see many blast forms and promyelocytes, characteristic of what is called "maturation arrest." Then, with recovery, the more mature forms began to develop until there was return to a normal marrow. In the patient going on to death there might be complete disappearance of the myeloid cells, with the remaining leukocytes consisting primarily of small mature lymphocytes along with some plasma cells.

The treatments which were recommended then, and are even recommended in some texts today, were varied. They all had one basic thing in common in that all of them were advised and used without having the benefit of a control group of untreated patients for comparison. Consequently no one actually knew what the mortality rate for the untreated patients was, and one could hardly expect it to have been higher than the rate in some of the series of treated patients. Among the various methods or agents recommended for treatment were transfusion, leukocyte cream, typhoid vaccine, the production of sterile turpentine abscesses, radiation of long bones, yellow bone marrow, liver extract, PENTNUCLEOTIDE®, adenine sulfate and folic acid. All of these were reported as reducing mortality but no one demonstrated that they had any specific effect on the marrow; in my own opinion they had none and were absolutely useless and even dangerous to the patient in some instances.

During this period Kracke[2] became imbued with the idea that benzene ring derivatives were responsible for this condition and carried out a good deal of experimental work trying to reproduce "acute granulocytopenia." Then in 1934 Madison and Squier[3] reported their cases of aminopyrine-induced granulocytopenia. Following this the medical profession became much more drug conscious, and such drugs as aminopyrine rapidly lost favor so that today only an occasional preparation is found which still contains it. It was not long before many other drugs were reported as having this effect on the marrow in sensitive individuals.

We then moved on into the era of the sulfonamides. All of these produced granulocytopenia in the sensitive individual, although there would be reports of series of a hundred or more patients being treated by some specific sulfonamide without any deleterious effect on the blood. The inaccuracy of such reports is recognized when it is remembered that, as mentioned previously, experience with thousands of cases is required to demonstrate this sensitivity. As was perfectly proper, the occasional case of granulocytopenia did not militate against use of the drug since the risk from the drug was insignificant in comparison with the tremendous benefits and the reduction in mortality of infections treated with it.

Then in the early forties Dameshek and Wolfson[4] suggested the use of sulfone drugs in treatment of granulocytopenia to prevent secondary infection. It should be noted that this treatment was to prevent secondary infection and was not proposed with the idea that it would have any effect on the bone marrow. Although this was a brilliant idea and one which we use in principle today in giving protective treatment to these patients, it did

have possible medicolegal repercussions, for it would be hard to convince a jury that a drug which was capable of producing granulocytopenia itself should be used in treating a disorder produced by another closely related drug. However, today treatment by the antibiotics is believed to offer protection to certain individuals who might otherwise succumb to an infection. Nevertheless, treatment of the marrow itself along with stimulation of the myeloid cells remains right where it was at the beginning of this era 30 years ago.

The list of drugs incriminated has grown to be a very substantial one, and now that members of the aminopyrine group or drugs containing aminopyrine itself are again being recommended for treatment of rheumatoid arthritis, we need constantly to remind ourselves of the possible dangers of these drugs. It is going to require constant vigilance and attention to symptoms in order to avoid a possible disastrous result. One cannot depend simply on following the leukocyte count while the drug is first being given, to tell whether there will be a toxic effect; we know from experience with aminopyrine that acute granulocytopenia may develop after weeks or even months of treatment and that this disorder can develop abruptly, with a normal leukocyte count having been present 12 or 24 hours before. My colleagues and I have already seen 2 cases of acute granulocytopenia attributable to drugs of this kind; in 1 of these cases the drug, 4-aminoantipyrine, was being used purely on an experimental basis but in the other case the drug used, phenylbutazone (BUTAZOLIDIN®), has been widely publicized and is now available to the medical profession. In my opinion the warning of the manufacturer that "counts of the red and white blood cells should be performed at weekly intervals, especially during the initial stages of therapy" should be radically revised and extended so that the physician is aware of all the warning signs of trouble at the earliest possible moment.

Examples of granulocytopenia secondary to use of drugs follow.

Case 1—A housewife, aged 28, was given four capsules of 4-aminoantipyrine daily for two months on an experimental basis to see if it would relieve her of rheumatoid arthritis. On July 1, 1952, sore throat, sore gums and blisters on the tongue developed. On July 2 the cervical lymph nodes were enlarged and the temperature rose to 102.6° F. On July 3 the leukocyte count was 2100 per cubic millimeter of blood, with practically no polymorphonuclear leukocytes. Physical examination disclosed marked gingival hypertrophy and redness, and moderate bilateral cervical adenopathy. Only protective treatment was given, consisting of 600,000 units of penicillin a day. The blood findings for succeeding days are given in Table 1.

TABLE 1

BLOOD COUNTS IN CASE 1

DATE	LEUKOCYTES		
	Total per cu. mm.	*Polymorphonuclear cells, per cent*	*Immature myeloid cells, per cent*
July 5	600	0	
" 6	850	0	
" 7*	1000	0	
" 8	900	0	
" 9	1300	2	
" 10	2200	18	10.5
" 11	2900	40	14
" 12	4100	17	28
" 14	9400	58	12

*Bone marrow aspiration.

Case 2—A male executive, aged 56, was seen September 29, 1952, because of rheumatoid arthritis of 20 years' duration. Since August 18, when the administration of cortisone had been discontinued, he had been unusually fatigued and had been taking three tablets of phenylbutazone (butazolidin) daily. He had continued taking the latter drug through September 27, omitting it only on September 26. On September 30 the patient said he felt as though he had "flu." More fatigue and aching had started the afternoon of September 29. The temperature was 101.2° F., there was no sore throat, the leukocytes numbered 600 on September 30 and

TABLE 2

BLOOD COUNTS IN CASE 2

DATE	LEUKOCYTES		
	Total per cu. mm.	*Neutrophils, per cent*	*Eosinophils, per cent*
September 29	1400		
" 30	600	0	30
October 1*	1400	0	8
" 2	900	0	4
" 3	1800	0	19
" 4	1050	0	14
" 5	1400	4	2
" 6	1600	2	
" 7	1100	14	
" 8*			
" 9	1300	14	
" 10	1600	19	
" 14	2600	21	
" 15	2400	20	

*Bone marrow aspiration disclosed on: October 1, only scattered progranulocytes and myeloblasts; October 8, 9 per cent myeloid cells and 2 per cent blasts, and October 15, marked increase in myeloid elements over October 8.

there were no polymorphonuclear leukocytes present. The blood counts for succeeding days are given in Table 2.

Not all cases of acute granulocytopenia are secondary to ingestion of drugs, and there are rare instances of severe acute granulocytopenia in which no etiologic factor can be found. Also, in some instances, severe leukopenia which at first sight may appear to be acute granulocytopenia is shown, on closer investigation, to be acute leukemia, splenic neutropenia or one of several other disorders. In some of these the clinical manifestation may simulate acute granulocytopenia because of the absence of neutrophils in both the peripheral blood and the bone marrow. Time does not permit a discussion of the differential diagnosis of these various diseases.

A review of the "Quarterly Cumulative Index Medicus" for the past 30 years shows that a great many drugs have been involved in the production of granulocytopenia, most of which are shown in Table 3.

TABLE 3

DRUGS REPORTED TO HAVE PRODUCED GRANULOCYTOPENIA

Acetarsone
ALURATE®
AMINOPTERIN®
Aminopyrine
Aminothiazole
AMYTAL® compound
Aniline
ANTERGAN®
Arsphenamine
ATABRINE®
Benzene
Bismuth
CAUSALIN®
Chloramphenicol (CHLOROMYCETIN®)
Cinchophen
DDT® aerosol
Dimethylaminoethyl-phenothiazine (DIPARCOL®)
Dinitrophenol
Diphenylhydantoin (DILANTIN SODIUM®)
GANTRISIN®
Gold preparations
Iodochlorhydroxy-quinoline
MAPHARSEN®
Mercury compounds
MESANTOIN®
Methaphenilene (DIATRIN®)
Methyldiphenyl-hydantoin
Methylthiouracil
Neoarsphenamine
NEOPRONTOSIL®
Nitrogen mustard
NOVALDIN®
NOVALGIN®
Penicillin
Phenobarbital (?)
Phenylhydrazine derivative
PRESIDON®
PRONESTYL®
PRONTOSIL®
Propyl thiouracil
p-Sulfanilaminopyridine
PYRIBENZAMINE®
Quinine
Streptomycin
Succinylsulfathiazole
Sulfadiazine
Sulfaguanidine
Sulfamerazine
Sulfanilamide
Sulfapyridine
Sulfarsphenamine
Sulfathiazole
TAPAZOL®
Thiosemicarbazone preparation (tibione)
Thiouracil
Thiourea
TRIDIONE®

Thrombocytopenic Purpura

The second condition in which a marked disturbance of a single marrow element may occur is thrombocytopenic purpura. In every case of what is apparently essential thrombocytopenia careful inquiry must be made to reveal the possible ingestion of a drug that might have an etiologic relationship. The clinical and laboratory manifestations of sensitivity secondary to drug ingestion vary in no way from those in which no etiologic factor can be found. In this group of cases the thrombocytopenia and the purpuric manifestations may appear during the time of ingestion of the drug and disappear when the medication is stopped, or the symptoms and findings may not put in their appearance until

TABLE 4

DRUGS REPORTED TO HAVE PRODUCED THROMBOCYTOPENIC PURPURA

Acetarsone	Nitrogen mustard
Aminopyrine	Quinidine
Arsphenamine	Quinine
Benzene	Sedormid
Ergot	Stilbestrol
Gold salts	Sulfonamides

some time after medication has been given. The sedative, SEDORMID®, which was quite widely distributed to the profession a number of years ago, is an example of the former, and the gold salts an example of the latter. In cases of thrombocytopenic purpura secondary to the use of gold salts, improvement may be spontaneous, or splenectomy may have to be resorted to in the hope of bringing about recovery. The list of drugs involved here is not as extensive as that producing acute granulocytopenia but it is no less important.

The following is a case report of sensitivity to sedormid.

Case 3—A man 62 years old came to the Mayo Clinic in August 1936 complaining of mild petechiae, bleeding from the gums and gross bleeding into the urine of three months' duration. The patient admitted frequent use of sedormid.

Mild petechiae were observed on physical examination. Results of the tourniquet test were positive. The spleen was not palpable.

The hemoglobin determination, erythrocyte count and leukocyte count were within normal limits. The platelet count was 80,000 per cubic millimeter. Clot retraction was normal. The bleeding time was three and a half minutes, and the coagulation time was five minutes. Platelets were found with difficulty on study of the stained blood smear. The patient was advised to discontinue the use of sedormid. Two weeks later he reported clinical improvement, and the platelet count was 226,000. The patient reported by letter in April 1945 that he had had no recurrence of his purpura and submitted reports of blood studies, the results of which were all within normal limits.

Table 4 lists drugs which have been implicated in the production of thrombocytopenia.

Hemolytic Anemia

The third type of disorder of the blood which may be secondary to use of a drug is hemolytic anemia. Here we have a type of reaction which may be precipitated acutely or may have a more gradual but also more chronic course. The characteristic findings are evidences of increased blood hemolysis as shown by increased indirect-reacting serum bilirubin, increased reticulated erythrocyte count as evidence of increased blood formation, hyperplastic marrow, increased fecal excretion of urobilinogen, and commonly splenomegaly of varying degree. Here as in all the other conditions of this group the patient needs to be questioned repeatedly as to possible contacts with noxious agents, however innocent-appearing they might be, and knowledge on the part of the questioner as to all the possible drugs involved is essential.

Practically all instances of hemolytic anemia secondary to the use of sulfonamide drugs have occurred during the febrile course of the illness for which the sulfonamide was given. Withdrawal of the drug resulted in improvement, although transfusions were at times used as supplementary treatment to hasten recovery.

Table 5 lists the drugs reported to have produced hemolytic anemia.

TABLE 5

DRUGS REPORTED TO HAVE PRODUCED HEMOLYTIC ANEMIA

Acetophenetidin	Phenothiazine
Ammonia	Phenylhydrazine
Arsphenamine	PLASMOCHIN®
Hydrogen arsenide	p-Phenylenediamine
Hydroquinone	Quinine
Monomethyl-p-aminophenol sulfate	Sulfonamides

Leukemia-like Disorders

The fourth group of unusual hematologic reactions are those in which a leukemia-like

picture may develop. Fitz-Hugh[5] has reported the occurrence of monocytic leukemia after the ingestion of aminopyrine (PYRAMIDON®). My colleagues and I have seen blood pictures identical with those of chronic myelogenous leukemia which were part of a general reaction after ingestion of a sulfonamide. These were not pure reactions in the sense that a single cell line was involved as in the cases of granulocytopenia or thrombocytopenia, and in at least some instances there was associated anemia, probably on a hemolytic basis. Marked enlargement of the spleen may be associated with these findings. However, as in the other groups, spontaneous cure frequently occurs.

Leukemia-like pictures have been attributed to the drugs listed in Table 6.

TABLE 6

DRUGS REPORTED TO HAVE CAUSED LEUKEMIA-LIKE DISORDERS

Leukemoid reactions
Aminopyrine
Arsphenamine
Benzene
Quinine
Sulfonamides
Leukemia
Benzene (C_6H_6)

Disturbances Due to Hair Dyes

In 1935 Baldridge[6] reported a group of 3 cases of macrocytic anemia, thrombocytopenia and varying leukopenia. He felt that there was a possible relationship between the hematologic disturbance and the hair dyeing and permanent waving to which these women had been subjected. The macrocytic anemia did not respond to large amounts of potent liver extract, but a perfectly normal blood picture gradually developed in the 3 women. Recently my colleagues and I encountered a case of this type in which the use of hair bleach, dye and permanent waving may very well have been an etiologic factor if Baldridge's[6] premise is correct.

Case 4—A housewife, aged 44, was seen October 14, 1952, because of a complaint of ecchymosis of four months' duration. Blood smears examined in July and early October were reported as disclosing macrocytic anemia, leukopenia with relative lymphocytosis and thrombocytopenia. Sternal aspiration revealed relative hyperplasia of the marrow. The detailed findings were reported to be as follows: hemoglobin 11.2 gm. per hundred cubic centimeters, erythrocytes 3,440,000 and leukocytes 3300 per cubic millimeter, differential count in percentages: lymphocytes 54.5, monocytes 9, neutrophils 34, eosinophils 0.5 and basophils 2; reticulated erythrocytes 1.5 per cent; platelets 45,000 per cubic millimeter and bleeding time 7½ minutes. Our examination of blood smears and bone marrow confirmed these findings.

No antibiotics had been used and no drugs had been ingested. From 1936 to 1946 the patient had used henna rinse frequently. From 1946 to the time of admission she had had hair bleach and tint at intervals of three or four weeks, and a permanent wave every three or four months.

This patient has had treatment with folic acid, vitamin B_{12}, ascorbic acid and other hematinics without effect. Since her blood has remained unchanged for a period of more than three months, it seems quite possible that recovery may possibly occur or she may continue at her present level, as occasionally happens.

Aplastic or Hypoplastic Anemia

The last group of cases to be discussed deserves special emphasis, for this group, at the present time, carries by far the highest mortality rate. In these patients there is a generalized effect on the marrow that results in a hypoplastic or aplastic marrow. Since the period between administration of the drug and the onset of symptoms or changes in the blood picture is frequently fairly long and since the reaction is rarely of an acute nature, there is as yet no means at the disposal of the physician whereby he can recognize indications for withdrawal of the drug and thereby prevent the development of the bone marrow changes or, insofar as is known, even amelio-

rate the course of the toxic effect on the marrow. The hematologic illness of the patient may begin in a variety of ways. The two most common ways, in our experience, are (1) with the onset of fatigue and weakness as the direct result of the development of varying degrees of anemia and (2) with the onset of purpuric manifestations as the result of thrombocytopenia.

The most recent drug to cause aplastic or hypoplastic anemia is the antibiotic, chloramphenicol (CHLOROMYCETIN®). Because of the therapeutic importance of this preparation we must exercise caution and restraint in condemning it. The general experience of observers reporting cases of aplastic or hypoplastic anemia that occurred after administration of chloramphenicol has been this: Symptoms may be observed after the giving of a single course of medication, or there may be no apparent deleterious effect after the first course of treatment but on repetition of treatment at some later date the symptoms and findings described are noted. These patients run the varying course seen in aplastic anemia, some of them having febrile episodes, others having profound weakness without purpura and still others having purpuric manifestations that dominate the picture. In our study of these patients my colleagues and I have not been able to formulate any criteria which tell us definitely whether a given patient has such a badly damaged marrow that recovery will or will not occur. In some of the cases the mildness of the changes in the peripheral blood made us feel that recovery should occur even though the marrow was severely involved, yet in these cases the changes in the blood became increasingly severe and the disorder proved fatal.

It is particularly difficult to make a prognosis in this condition. It seems likely that the bone marrow picture is a better guide as to the outcome than the peripheral blood picture. It is of course to be remembered that there may be a delay in erythrocytic changes and that the erythrocyte count may not immediately reflect the marrow picture because of the great average longevity of the erythrocyte. Up to the present time we have encountered 16 cases of aplastic anemia in which chloramphenicol appeared to be the causative agent. In 10 of these death occurred, in 2 there has been apparent recovery and in the rest the final result has not been determined.

TABLE 7

DRUGS REPORTED TO HAVE CAUSED APLASTIC OR HYPOPLASTIC ANEMIA

Acetarsone	Neoarsphenamine
Acetophenetidin	Nitrogen mustard
Arsphenamine	Penicillin
BENZEDRINE®	Phenacetyl urea
Benzene	Phenylethylhydantoin
Bismuth	Quinacrine dyes
Diphenylhydantoin sodium	Streptomycin
Estradiol benzoate	Sulfapyridine
Ethyl urethane	Sulfarsphenamine
Gold salts	Sulfathiazole
Hydantoin	Tar
Mapharsen	TENEBRYL® (iodine preparation)
Mercury	THEROTRAST®
Mesantoin (methylphenylethylhydantoin)	TNT
METRAZOL®	Tridione
Naphthalene	Urethane
	Xylene

Drugs such as chloramphenicol should not, in my opinion, be used if there are other antibiotics with the same general effect. Chloramphenicol should be restricted to the treatment of typhoid fever and to those staphylococcic infections that are not affected by other antibiotics but that are sensitive to chloramphenicol. The warning of the manufacturer that blood counts should be made frequently to avoid this difficulty cannot be said to be effective in avoiding reactions since, as has been mentioned, the changes in the blood do not develop as an acute reaction but frequently occur late after recovery from the infection for which the drug was given. This type of reaction has been described before, particularly in patients exposed to benzene vapor.

The following is an example of aplastic anemia due to chloramphenicol.

Case 5—A 3 year old white girl had a history of easy bruising and of having had two episodes of epistaxis during the preceding two weeks. Examination disclosed the following:

hemoglobin, 9.2 gm.; erythrocytes, 5,030,000; leukocytes, 1700 to 6000; lymphocytes, 95 to 97 per cent, and monocytes, 1 to 3 per cent. Sternal aspiration revealed marked hypoplasia. The daily temperature was 103 to 104° F. The patient died on the ninth day after admission, and postmortem examination disclosed hypoplasia of the bone marrow.

During the three weeks prior to onset of the hemorrhagic tendency, the patient had received 20 capsules of chloramphenicol because of pharyngitis.

Table 7 lists the various drugs reported as producing aplastic anemia.

Summary and Conclusions

Drug therapy can be definitely incriminated in the reproduction of practically every known type of blood dyscrasia. In the introduction of new drugs one must consider critically their possible effect on the blood and bone marrow. Careful observation of and report on the blood changes that occur in the ordinary number of cases reported in trials of drugs cannot be considered an adequate basis for determining whether a particular drug has a harmful effect, since sensitivity to any of these drugs is very uncommon. When there is a choice among several drugs, all of which have the same therapeutic effect but one of which affects even the occasional patient in a harmful manner, it seems reasonable to ask that the harmful drug be excluded from consideration in therapy. Many drugs which may have a damaging effect on the bone marrow are being used in practice every day. As long as these individual drugs are the only ones available for a specific purpose and the risk from the disease being treated is greater than the risk of using the drug, then the physician is warranted in taking the "calculated risk" involved.

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Postgraduate Clinical NOTES

4. TORSION OF SPERMATIC CORD

The most striking symptom of torsion of the spermatic cord is the sudden onset of severe, unrelenting testicular pain. The pain is usually well localized, but may radiate to the groin or flank. Unlike the pain in inflammatory conditions of the intrascrotal contents, it is not relieved by elevation of the scrotum (Prehn's sign). The pain is so severe that medical attention is sought immediately. In the author's experience, this was an important consistent finding. There may be nausea and vomiting. The temperature is slightly elevated or normal. There is marked prostration, seemingly out of proportion to the pathologic process.

Fletcher, et al., *American Journal of Roentgenology*, December 1952

Intestinal Obstruction

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While it is relatively easy to recognize a large, strangulated intestinal obstruction, in many cases small, localized areas of necrosis cannot be diagnosed with any degree of certainty. Ideal treatment in any case consists of (1) adequate administration of fluid and electrolytes, (2) surgical exploration and (3) excision of devitalized bowel and restoration of gastrointestinal continuity when gangrenous intestine is found at operation.

ONE hesitates to discuss a subject about which so much has been written. However, a survey of recent trends in treatment of intestinal obstruction indicates to one that such a presentation is justified.

W. C. MAC KENZIE

A study of the overall mortality rate for intestinal obstruction since 1925 is of interest. For the province of Alberta, there is a plateau in the mortality curve from 1925 until approximately the mid 1930's, at which time there seems to be an improvement in the picture—coinciding with the advent of intestinal intubation and the sulfonamide drugs. This improvement continues until recent years, when a rise is noted.

More than one factor is responsible for this increased mortality rate. The diagnosis of congenital atresia and stenosis of the gastrointestinal tract has been made more frequently, and these lesions carry a high mortality rate. However, we feel that another factor is the use of intestinal intubation and antibiotics not as adjuncts to treatment, as they should be used, but as the treatment per se for intestinal obstruction in some cases in which this form of expectant treatment is ill-advised. This fact was brought home to us very clearly in our hospital a few years ago. A patient who eventually underwent operation had for several days been treated by means of antibiotics and intubation; at operation a small area of strangulated bowel was found which we apparently were unable to detect preoperatively. This patient had none of the classic signs of strangulation such as tenderness, rebound tenderness and rigidity, and we were once more reminded that it is relatively easy to diagnose a large, strangulated obstruction but that a small, localized area of necrosis cannot be diagnosed with any appreciable degree of certainty.

Intestinal obstruction so frequently is of a dramatic nature and so often causes death that there is a tendency to consider it a disease entity. It is, however, only a symptom, and may have diverse causes. Therefore the clinical manifestations vary with (1) the mechanism of production, (2) the portion of the bowel involved and (3) the complications

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

which may develop. Another tendency is to classify each case of intestinal obstruction as either a simple occlusion, a strangulation obstruction or a neurogenic obstruction. If each case could be so classified, life would be much simpler for the surgeon called on to care for the patient with an acute abdominal condition. However, it becomes increasingly clear that no such dividing line can be drawn and that in many cases varying degrees of all three types will be seen. For example, in a case of band obstruction there may be a simple obstruction proximal to the band and strangulation at the actual site of the band if the pressure is prolonged, and after a long period of simple obstruction in the proximal loop, neurogenic obstruction may supervene.

Incidence

The incidence of the various forms of intestinal obstruction is difficult to estimate. McIver's report from the Massachusetts General Hospital in 1933 provides a good cross section of the average large general hospital for that year. Mersheimer and Winfield in 1952 reported on a similar group of patients, and the incidence of each of the various forms of obstruction varies somewhat from the earlier report by McIver (Table 1). Such differences can be explained by examining the data concerning the various lesions. At present many more people have hernial repairs before strangulation develops, so this group is bound to be decreased in size. Similarly, more abdominal operative procedures are being done, which means that the incidence of bands and adhesions is inevitably increased. Also, diagnostic facilities have improved and people have a longer life span; thus neoplasms comprise a greater portion in recently reported series.

TABLE 1

INCIDENCE OF VARIOUS TYPES OF INTESTINAL OBSTRUCTION

	McIver, 1933 (per cent)	Mersheimer and Winfield, 1952 (per cent)
Strangulated external hernias	44	25
Bands and adhesions	30	34
Neoplasms	10	16
Intussusceptions	5	4
Volvulus	4	4
Other	7	17

Pathophysiology

The pathophysiologic alterations in cases of intestinal obstruction can be grouped under five headings: (1) fluid and electrolyte losses, local and systemic; (2) distention, its effect on function and viability; (3) toxicity; (4) bacterial growth, its relation to intestinal viability, and (5) problems attending compromise of intestinal blood supply.

The effects of obstruction may be either local (on the bowel wall itself) or general (on the body as a whole), and the proportion of effect, either local or general, depends on (1) the level at which obstruction occurs, (2) the degree of increase of intraluminal pressure and the length of time this pressure is maintained and (3) the maintenance of blood supply to the intestine.

Obstruction high in the small intestine causes important chemical changes in the blood. Vomiting is an early symptom and is continuous, and the bowel is emptied. Distention is not an important factor in obstruction at this level. The electrolyte loss, however, produces striking systemic effects: Dehydration, oliguria, hemoconcentration, hypocalcemia, hypopotassemia, alkalosis and a rise in nonprotein nitrogen all result from the continuous vomiting (Figure 1). Administration of electrolytes delays the general or systemic effects of high intestinal obstruction and may prolong life, but will not appreciably alter the course of obstruction which develops low in the small intestine.

When obstruction occurs low in the small bowel, vomiting cannot empty the bowel completely, fluid and gas accumulate in the small bowel and distention becomes a marked feature (Figure 2). What causes the distention? We know that approximately 8000 cc. of fluid is secreted daily including saliva, gastric juice, bile, and pancreatic and intestinal juice. We know also that a considerable quantity of gas

FIGURE 1. HIGH SMALL BOWEL OBSTRUCTION. Distention is not an important factor in obstruction high in the small intestine, but the continuous vomiting results in electrolyte loss which produces dehydration, oliguria, hemoconcentration, hypochloremia, hypopotassemia, alkalosis and a rise in nonprotein nitrogen. Administration of electrolyte solutions delays the effects of high obstruction.

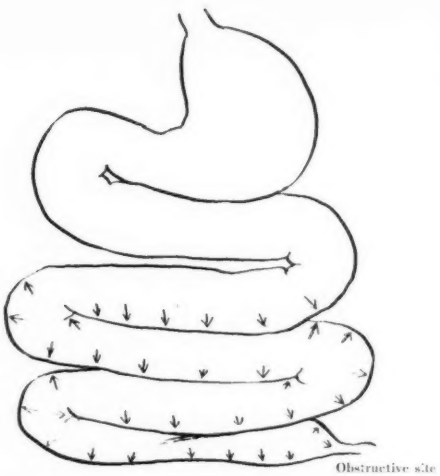

FIGURE 2. LOW SMALL BOWEL OBSTRUCTION. Vomiting cannot empty the bowel completely in cases of obstruction low in the small intestine. Fluid and gas accumulate, and distention becomes a marked feature. Administraiton of electrolyte solutions will not appreciably alter the course of such obstruction.

is present in the distended small intestine. Wangensteen and others have demonstrated that approximately 70 per cent of this gas is swallowed air; the remaining 30 per cent, of course, originates in the body.

The role of bacteria in low bowel obstruction is important. It is well known that the lower the obstruction, the greater the distention. With this increased distention there is a greater incidence of hemorrhage, necrosis and ulceration. It has been proved experimentally that antibiotics in large doses may reduce or prevent these mucous membrane changes. Thus we can assume that (1) distention helps the invasion of the bacteria into the intestinal wall, and (2) bacterial growth may be responsible for ulceration and necrosis.

Although fluid and electrolyte loss is known to be responsible for the systemic effects and subsequent death in unrelieved high small bowel obstruction, the mechanism in low small bowel obstruction is not well understood. The consensus today is that prolonged distention produces thinning of the bowel wall with compression of intramural circulation. This thinning in turn produces anoxia with vascular impairment of the intestinal wall, leading to loss of viability and to mucosal ulceration. If perforation occurs it is easy to understand the lethal transperitoneal absorption following this catastrophe. If perforation does not occur we hypothesize that increased permeability occurs with the transudation of toxic bacterial products into the peritoneal cavity, and that resultant absorption of these products from the peritoneum causes death (Figure 3).

Obstruction of the colon produces a closed loop in a high percentage of cases because the ileocecal valve permits ileal contents to enter the colon but does not allow regurgitation into the ileum (Figure 4). In other words, there is a closed loop between the ileocecal valve and the obstruction, which is usually a neoplasm of the left colon. A sliding left inguinal hernia or a volvulus of the sigmoid may produce strangulation obstruction in contradistinction to a neoplasm, which usually produces a simple obstruction.

Strangulation adds materially to the dan-

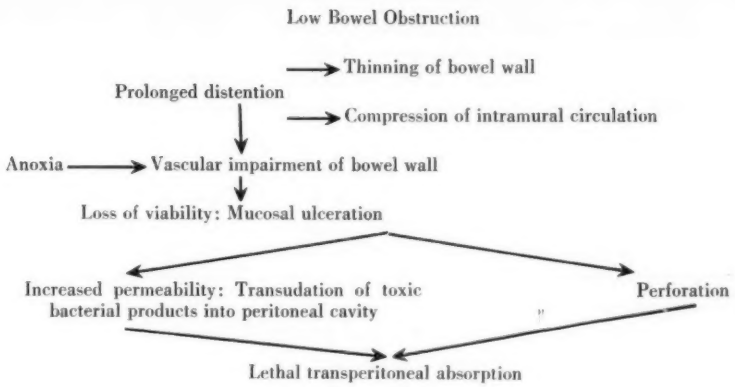

FIGURE 3. Summary of the consensus concerning the mechanism responsible for the systemic effects and subsequent death in cases of unrelieved obstruction low in the small intestine.

gers of obstruction, due primarily to the ready passage of bacteria or toxic material through the necrotic intestinal wall which results. Pure arterial obliteration rarely occurs in humans. In cases of strangulation, venous occlusion usually is part of the pathologic picture. In a large strangulation obstruction, loss of whole blood into the bowel wall and lumen may be sufficient to cause marked shock and early death.

Clinical Picture

Pain usually is the first consistent and the most important symptom in all except paralytic cases. Occlusion produces pain which is crampy, colicky and central in location and occurs in waves lasting three to five minutes. It becomes very severe and then passes off to be followed after a period of freedom by a return of the pain at more or less regular intervals. In simple occlusion the onset of pain may be more or less gradual.

The pain of strangulated obstruction is of sudden onset. It may penetrate to the back, but for the most part it is diffuse and usually increases in severity and becomes continuous.

High intestinal obstruction usually produces pain which is referred to the upper abdomen, whereas low obstruction results in pain in the central or lower abdomen. In colonic obstruction the pain usually has been present for weeks or months as a mild, crampy disturbance across the lower abdomen. Relief is often obtained by passing gas or by a bowel

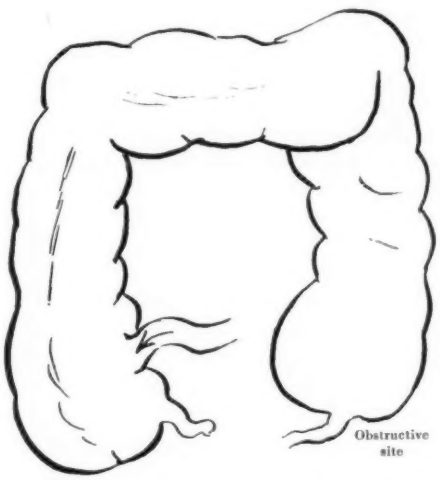

FIGURE 4. COLON OBSTRUCTION. A closed loop is produced in a high percentage of cases of obstruction of the colon because the ileocecal valve permits ileal contents to enter the colon but does not allow regurgitation into the ileum.

movement, indicating an incomplete obstructive process. However, when the obstruction becomes complete the pain becomes more severe and generalized, and the intervals between colicky attacks are much longer than in cases of small bowel obstruction. A surprising finding at operation often is an annular carcinoma of the low descending colon or sigmoid with no apparent lumen in a case in which there had been no difficulty prior to the onset of the acute attack.

Complete constipation is the rule in all cases of complete obstruction, and flatus is not passed after the onset of symptoms. Immediately following the onset there may be one bowel movement, emptying the bowel below the obstruction, or a diagnostic enema may result in the return of a small amount of stool, but no flatus.

Vomiting is an early symptom in high intestinal obstruction and may occur shortly after onset of pain or simultaneously with the colic. In low small bowel obstruction it begins later, perhaps four to six or even eight hours after onset of symptoms. However, vomiting occasionally begins one and one-half hours after the first symptoms of low ileal obstruction. Colonic obstruction, on the other hand, may not produce vomiting for three or four days, and patients frequently are seen who have not vomited despite a long-standing large bowel obstruction. Strangulation is accompanied by persistent, copious vomiting, with peristaltic exacerbation.

Physical examination—There may be little alteration in the patient's general appearance during the early stages of intestinal obstruction. However, as the disease progresses the findings include a dry tongue, dry lips, sunken eyes and the parchment-dry skin resulting from dehydration. These findings, together with the complaint of thirst and a history of vomiting, are the most reliable evidence of dehydration.

Abdominal findings—In high small bowel obstruction, upper abdominal distention may be slight or absent, while considerable distention accompanies obstruction in the lower portions of the small bowel, with the exception of occasional cases of gallstone ileus. Peripheral distention is seen early in colonic obstruction, with superimposed central distention resulting later as the low small bowel dilates.

Abdominal scars should be inspected carefully. Bear in mind that in most large series of cases of intestinal obstruction approximately 65 to 75 per cent originate from (1) bands or adhesions from previous operations or (2) involvement of a hernial site.

Simple occlusion may produce few abdominal symptoms, whereas tenderness, rebound tenderness and spasm are of great importance in making a diagnosis of strangulated obstruction. If a patient has had an obvious simple occlusion, these findings later in the course of the disease indicate compromise in the blood supply to the affected part. A tumor mass in the left lower quadrant in an elderly person certainly points to malignancy as the etiologic factor. A sausage-shaped swelling in the right upper quadrant, left upper quadrant or left lower quadrant in a child suggests intussusception. Abdominal palpation may reveal the tense, tympanitic, tender balloon of volvulus.

Auscultation of the abdomen with a stethoscope discloses the metallic explosions of the shifting gas or the bubbling and gurgling of mixed gas and fluid, the highest pitch of these sounds corresponding to the height of the crampy pain in obstruction, sound occurring just before the pain. In cases of strangulation obstruction or in late stages of simple occlusion, auscultatory sounds may disappear. One of the diagnostic features of adynamic ileus is the absence of intestinal sounds—the "silent" abdomen.

Except in the presence of extensive strangulation, there is little deviation from normal in the pulse and temperature. The white blood cell count is elevated in cases of strangulation, but this finding does not confirm the diagnosis because leukocytosis frequently accompanies an ordinary simple occlusion.

Roentgenographic findings—A scout film of the abdomen is a valuable aid in diagnosing intestinal obstruction. Normally an infant exhibits gas in the stomach, duodenum and jejunum 6 to 15 minutes after birth. The same infant will have gas in the sigmoid and rectum six hours after birth, and until about 18 months of age will have an equal distribution of gas in the small and in the large bowel. Up to the age of 6 years there will be less gas in the small intestine than in the large, but after 7 years of age no gas is present in the small bowel. Wangensteen and others have shown that this gas in the small bowel is mixed with fluid and travels too quickly through the small bowel for collections of

gas to be demonstrated. However, when the progress of bowel content is delayed, i.e., if stasis in any form is present, distended, gas-filled loops are easily detected.

In simple occlusion of the small bowel these gas-filled loops tend to be centrally located and to assume a more or less transverse position in the abdomen. In high intestinal obstruction the valvulae conniventes of the jejunum outlined by gas may simulate closely the colonic haustrations; however, the central, horizontal position serves to distinguish them in most cases. In low small bowel obstruction the loops present a ladder pattern with loops of ileum, cylindric and free from valves, readily distinguished from jejunum or colon. In large bowel obstruction the distended peripheral loops of bowel tend to be vertical in direction. These may be diagnostic and the level of a colonic obstruction sometimes can be determined accurately by a scout film. In volvulus of the cecum or sigmoid the enormously dilated lumen of the bowel takes a central position.

Approximately two-thirds of all colonic obstructions present conclusive roentgenographic evidence of the presence and the level of obstruction. It is unnecessary for me to reiterate that barium must not be given orally when there is suspicion of an obstruction. Barium may be given through an intestinal tube such as a Miller-Abbott or Cantor tube, using a small amount. May I add here that barium enemas may be hazardous. We observed one patient recently in whom barium passed a sigmoid obstruction, apparently under some pressure, and was extremely difficult to remove, even after a transverse colostomy. Many authorities use barium enemas to reduce intussusception and claim a high percentage of reductions. They point out that, when possible, the terminal ileum must be filled with barium, and these workers are convinced that many operative procedures can be prevented through the careful use of this diagnostic procedure without high pressures. Our own experience has not been as satisfactory, and we have lost some of our enthusiasm for this conservative measure.

A carefully taken history, a detailed physical, rectal and sigmoidoscopic examination, and scout films usually provide sufficient evidence for the diagnosis of intestinal obstruction.

Treatment

In the absence of strangulation, control of distention by constant suction often will effect release of the obstructing mechanism. However, because strangulating lesions sometimes exhibit no evidence of their presence, exploration is indicated in nearly all cases of obstruction of the small bowel. Exploration should be done as quickly as possible in cases of simple occlusion of the small bowel, if the patient is seen within 24 hours after the onset of symptoms. If 72 hours or more have elapsed since the onset of symptoms, and if there is no evidence of strangulation, the patient should be prepared carefully. Time spent in relieving the distention by intubation, in correcting fluid balance, hypoproteinemia, etc., and in administering blood and intravenous fluids more than compensates for the delay in surgery. In the absence of strangulation, the response to conservative therapy usually is satisfactory if the condition is not irreversible.

When strangulation is suspected, operation is mandatory. In such a patient it will be difficult to pass an intestinal tube, and the response to conservative measures is poor.

Many patients with colonic obstruction will respond to conservative measures—hot rectal irrigations, heat to the abdomen, etc.—but if these fail, decompression must be effected either by cecostomy or by transverse colostomy. I cannot leave the subject of conservative therapy without mentioning the use of the rectal tube threaded into the sigmoid volvulus through the sigmoidoscope. This ingenious and useful procedure may guide patients over the acute episode so that they may be prepared for definitive surgery.

When surgical intervention is decided on, suction provides a valuable adjunct to treatment by partially reducing the distention preoperatively and by preventing further distention postoperatively.

Experience has shown that the conditions in which intestinal decompression is of value

as a therapeutic measure are (1) adynamic ileus, postoperatively or otherwise, and (2) recent postoperative nonstrangulating obstructions due to fibrinous adhesions.

Charles Johnson of Detroit, who has made many contributions in this field, stated recently that the only operation indicated in neurogenic or adynamic obstruction is a small incision in the abdominal wall to guide the intestinal tube through the pylorus and down into the small bowel if it will not go down any other way.

Because 36 per cent of cases of intestinal obstruction are due to bands and adhesions, we might ask the question, What can we do to avoid abdominal adhesions? Of the many measures employed in attempts to prevent adhesions, probably the one which has had the most persistent use is heparin. However, this is not without a very great risk, Boys in 1942 and Lord in 1949 each having reported deaths from the use of heparin intraperitoneally. Also, several observers have proved it to be a definite cause of hemorrhage in the experimental animal. Hyaluronidase, ACTH and cortisone have been used experimentally but their clinical application is not yet generally accepted.

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MEETINGS AND POSTGRADUATE COURSES

Oak Ridge Institute of Nuclear Studies, Special Training Division: Advanced course in autoradiography, June 15-25, intended for research level personnel using or planning to use this technic. Three basic courses in radioisotope technics, each of four weeks' duration, will begin on June 8, July 6 and August 10. Additional information may be obtained from Special Training Division, Oak Ridge Institute of Nuclear Studies, P.O. Box 117, Oak Ridge, Tennessee.

University of Minnesota Medical School, Minneapolis: Continuation course in gynecology, for specialists, April 16-18, at the Center for Continuation Study. This is the course which originally was scheduled for December but which had to be cancelled. Dr. John L. McKelvey is director.

Continuation course in gastroenterology for general physicians, April 27-29, at the Center for Continuation Study. Visiting faculty will include Dr. Chester M. Jones of Harvard University Medical School, who will deliver the Jackson Lecture April 28. Course is presented under the direction of Dr. C. J. Watson.

Eighth International Congress on Rheumatic Diseases. Geneva, Aix-les-Bains and Zurich, August 24-28, 1953. Reservations may be addressed to Professor K. M. Walthard, Institut de Physiatrie, Cantonal Hospital, Geneva, Switzerland. Information about the trip and lodgings may be obtained from the American Express Company.

American College of Surgeons: The following courses are offered through the cooperation of the directors and the institutions at which they will be given:

Cardiovascular diseases, April 27-May 2, at American College of Physicians building, Philadelphia, and Philadelphia institutions. Dr. William G. Leaman, Jr., director.

Controversial issues in internal medicine, May 11-16, at Pennsylvania Hospital, Philadelphia. Dr. Garfield G. Duncan, director.

Electrocardiography: Basic principles and interpretation, May 11-16, at Massachusetts General Hospital, Boston. Dr. Conger Williams, director.

Internal medicine: Important refinements of diagnosis and treatment, May 18-22, at University of Oregon Medical School, Portland. Dr. Howard P. Lewis, director.

American Society of X-Ray Technicians: First international convention of x-ray technicians, June 28-July 2, at the Royal York Hotel, Toronto, Canada. Meeting arranged jointly by the American Society of X-Ray Technicians and the Canadian Society of Radiological Technicians.

American Academy of Pediatrics: Areal meeting, April 20-22, at Hotel Statler, Boston.

Comments on Podalic Version and Extraction

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In properly selected cases, podalic version is one of the most valuable means of delivery at our disposal. It should be done only when proper indications and conditions essential to its safe performance are present. To ignore these is to invite disaster. It does not and should not come into competition with the use of low or mid forceps. In its admittedly limited field of application, it is a valuable procedure which is safe for mother and child.

I WOULD like to preface my remarks by quoting an aphorism enunciated by one of my former chiefs, Dr. Walter Chipman: "If it is important to be in the world at all, and most of us act as though it were, the manner and safety of our entrance are surely of first consideration."

Podalic version, of course, might well be one mode of entrance into this world.

With the broadening of the indications for cesarean section and the increased safety in its performance, the employment of podalic version is decreasing. This would seem to be a pity, because in certain instances podalic version would seem to be the ideal mode of procedure and should be well able to withstand competition with cesarean section in properly selected cases.

Podalic version is an ancient procedure, its exact period of origin being lost in the mists of antiquity. It is believed to have been employed in Hippocratic times, but fell into desuetude until it was revived by Ambroïse Paré in the sixteenth century. Its use reached a peak in the hands of Potter of Buffalo, who delivered a high percentage of his patients in this manner, his objective being the abolishment of the second stage of labor.

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

Indications and Contraindications

The indication par excellence for podalic version is a transverse presentation (Table 1), which occurs in only about 0.5 per cent of all obstetric cases. This is a situation in which the birth of a full term child is to all intents and purposes impossible and artificial interference in some form is essential. The indication may be for cesarean section, particularly in primiparous women, when the faulty presentation may be the result of an abnormal pelvis which has prevented the proper engagement of the head. However, most transverse presentations occur in multiparous women and most are the result of lax abdominal walls in the presence of a normal pelvis. Under such circumstances if the position of the child cannot be changed by exter-

TABLE 1

INDICATIONS FOR PODALIC VERSION

1. Transverse presentations
2. Other abnormal presentations
   Oblique
   Face presentation with chin posterior
3. Prolapsed cord or extremity
4. Impending fetal asphyxia with the head high in the pelvis
5. To effect the delivery of the second child in a twin pregnancy when there is delay and when the child is presenting transversely or by the head

nal version before labor is well advanced, podalic version becomes the ideal procedure.

In this situation I let labor continue until the cervix is fully dilated, at which time the membranes are ruptured artificially and the version and extraction performed. Done under these conditions the procedure is easy to accomplish and safe for both mother and child. Should the membranes rupture when the cervix is partially dilated, dilatation of the cervix must be completed artificially before version and extraction are attempted. I might qualify that statement by saying that manual dilatation is not done when the cervix is dilated only 2 or 3 cm. (a colleague of mine calls this manual tearing of the cervix); but if the cervix is dilated to 6 or 7 cm. in a multiparous woman, generally speaking it is relatively safe to complete that dilatation and do podalic version.

The so-called neglected transverse presentation is a distinct contraindication to version. By neglected transverse presentation I mean one in which the membranes have ruptured, the cervix is partially or fully dilated, a prolapsed arm protrudes from the vulva, the shoulder becomes impacted in the superior strait, all the amniotic fluid is drained away and the uterus becomes tightly contracted around the body of the child. The end result in such a case, if neglected, is always the same—a rupture of the uterus with catastrophic effect on the child and probably on the mother as well.

Such a case came under my observation about 40 years ago, at which time I was associated with the late Dr. J. W. Williams. A primiparous woman in her early twenties presented an example of a neglected transverse presentation. The fetal heart sounds were excellent, and the woman's condition seemed pretty good. This was before the days of safe extraperitoneal section or even safe low cervical section, and I was faced with a tough situation. It turned out to be a very important and instructive case. I delivered this woman by cesarean section and followed that by removal of the uterus, which I feared might cause infection. The mother made an excellent recovery and the baby was perfectly healthy.

The record of that patient was brought out year after year for quite a long period of time by Dr. Williams and presented to students as a striking example of what not to do under such circumstances. We disagreed on that; I still think I did the right thing, and he continued to think that I did not. But it is a critical situation when it arises, and obviously podalic version cannot be given serious consideration in such a case.

Other abnormal presentations, such as oblique, persistent brow and face presentations with the chin posterior, may also present indications for podalic version and extraction. If the face is presenting with the chin obliquely or directly posterior, podalic version should not be attempted unless the head can be disengaged easily and the child turned with equal ease. You all know the risk of a face presentation with the chin obliquely posterior; it may rotate into the hollow of the sacrum, and there again is a situation in which delivery is impossible and, if nothing is done, the result will be rupture of the uterus.

As a prophylaxis against this posterior rotation of the chin, in a case of face presentation with the chin obliquely posterior, we usually feel justified in doing what we call a conversion, that is, simply flexing the head, when possible. Such a conversion may suffice. On the other hand, if this can be done and if conditions are favorable, we might perhaps just as well go ahead and complete the de-

livery by performing a podalic version. This, again, is a rare situation, but the method is valuable when the indication arises.

Oblique presentations usually are transient but occasionally may call for interference. The statements made concerning face presentations hold true also with regard to brow presentations.

In vertex presentations there may be need for immediate and rapid delivery. If conditions are favorable, some complications may be handled better by podalic version than by other procedures.

A prolapsed cord or extremity (so-called compound presentation) may well be a situation calling for immediate action. If the cord is prolapsed, obviously only a very limited time is available or the child will die. One great advantage of version in this situation is the speed with which it can be done, provided conditions are favorable for its performance. In compound presentations the prolapsed extremity, usually an arm, may cause serious dystocia, and again delivery by version and extraction may be the procedure of choice under favorable conditions.

Evidence of impending fetal asphyxia, with the head high in the pelvis, of course is an indication for immediate delivery if it can be done without undue risk to the mother. Version would be preferable to a high forceps operation, if conditions are favorable.

In certain cases (and this again is a very limited application) of antepartum or intrapartum hemorrhage, whether the result of placenta previa or of abruptio placentae, version may be the best procedure.

Podalic version may be indicated as a means to effect the birth of a second child in a twin pregnancy when the presentation is transverse or when the head is presenting. A delay of several days between the birth of a pair of twins is inexcusable and an example of bad obstetrics, and I mention it only to condemn it. Should there be delay in the birth of the second child, it ordinarily is very simple to rupture the second amniotic sac and turn and extract the second child with safety to both mother and child.

In a general way, podalic version is indicated in any complication where rapid delivery is essential and in any delivery which cannot be handled better by application of low or mid forceps.

TABLE 2

CONDITIONS TO BE FULFILLED BEFORE PODALIC VERSION MAY BE SAFELY ATTEMPTED

1. The cervix must be fully dilated, or the completion of dilatation easily effected
2. There must be no marked pelvic contraction or cephalopelvic disproportion
3. The presenting part must not be so firmly engaged that it cannot be disengaged easily
4. Sufficient amniotic fluid must be left in the uterus to permit easy turning of the child
5. A tightly contracted uterus is a definite contraindication

Conditions to Be Fulfilled

You undoubtedly have noticed that I have qualified the indications for podalic version with the phrase, "provided conditions are favorable." Proper attention must be paid to these conditions (summarized in Table 2).

1. The cervix must be fully dilated or easily dilatable. The child may be turned successfully through a partially dilated cervix, but extraction can result only in serious injury to the maternal soft parts and to the baby.

2. There must be no marked pelvic contraction or cephalopelvic disproportion. Again, the child may be turned successfully, but extraction can result only in serious injury or in death.

3. The presenting part must not be so firmly engaged that it cannot be easily disengaged from the pelvis. Undue force used to dislodge the presenting part may result in a ruptured uterus.

4. There must be sufficient amniotic fluid within the uterus to permit the easy turning of the child. It is impossible to put an exact time limit on the length of time after rupture of the membranes when version may still be carried out safely. The procedure may be difficult and dangerous when only an hour has

elapsed, or it may be safely executed after a much longer interval, depending on the degree of contraction of the uterus, the free motility of the child and the condition of the lower uterine segment. To attempt podalic version in the presence of a tightly contracted uterus or a thinned-out lower uterine segment is to invite disaster and will probably result in rupture of the uterus.

Unless these four conditions are present, podalic version is definitely contraindicated.

The great danger, of course, in podalic version is the possible rupture of the uterus, but if the indications are selected carefully and the conditions fulfilled, that danger should become practically nonexistent.

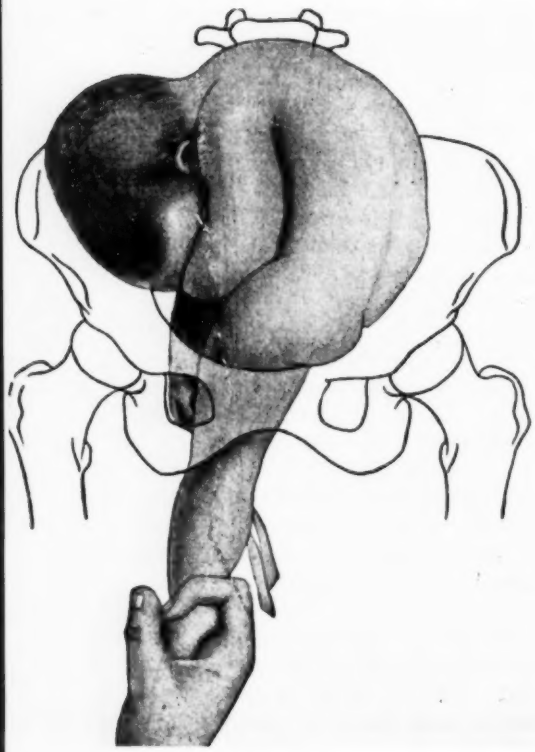

FIGURE 1. Version; transverse presentation, back posterior, seizure of upper foot.

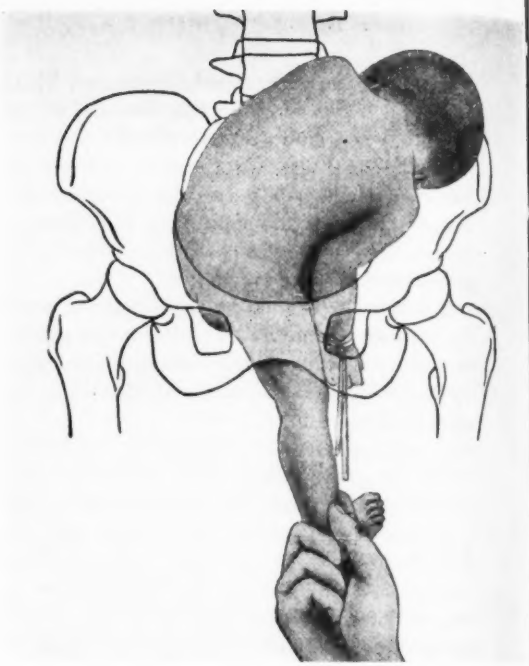

FIGURE 2. Version; transverse presentation, back anterior, seizure of lower foot.

(Figures 1 and 2 from Stander, H. J., "Textbook of Obstetrics," Ed. 9, courtesy Appleton-Century-Crofts, Inc.)

Technic

Deep anesthesia with complete relaxation is essential. Elbow length rubber gloves, as recommended by Potter, are a great help. Manual dilation of the outlet is performed. In transverse presentations, when the back of the child lies posterior, it is preferable to grasp the upper foot for traction (Figure 1). This prevents the chin from impinging on the symphysis during the extraction after the child is turned. For a similar reason, when the back lies anterior it is best to grasp the lower foot for traction (Figure 2). If both feet are easily accessible they may both be grasped; in fact, the procedure will be somewhat easier if this is the case.

When the child presents by the head, most textbooks advocate the use of the hand whose palmar surface corresponds to the abdomen of the child, and the grasping of the anterior foot for traction (Figures 3 and 4). Potter, to the contrary, uses the same hand no matter

what the presentation. I consider this a matter of choice.

Another point recommended by Potter is that the operator should grasp both feet of the child for turning and extraction. Having completed the turning, the extraction is just the same as in an ordinary breech presentation. The aftercoming head may be delivered by the Mauriceau maneuver or by the application of forceps, whichever method seems preferable, and episiotomy done if it seems to be desirable.

Potter's recommendation of grasping both feet to facilitate turning the child is an excellent one, but it did not originate with Potter. I would like to quote a paragraph from a book written by Edward Chapman and published in London in 1733—220 years ago: "The hand once introduced into the womb, you will presently perceive what part offers first. Whatever the picture is, you are (with as little force as possible) to reach for the foot. It is best (if possible) to take them both between your fore and middle fingers, and then draw them down into the vagina. As soon as you have the legs, you are to take them in a cloth and draw them gently down, ever observing that the toes of the child be turned towards the mother's back, that when it comes to the head, the chin may not stick or hang upon the os pubis."

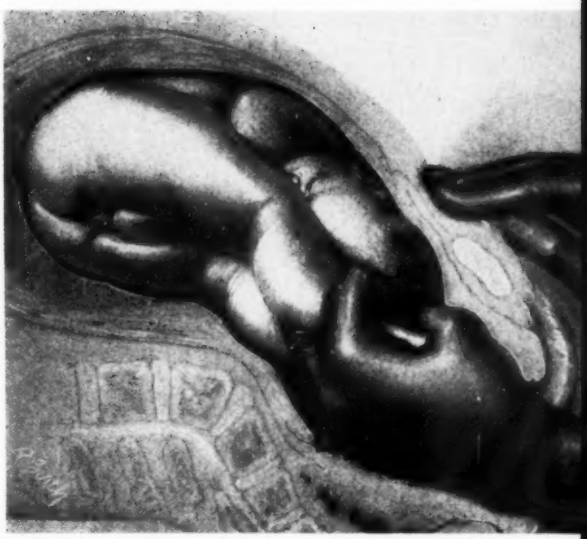

FIGURE 4. Internal podalic version. Upward pressure on head is made as downward traction is exerted on feet.

(Figures 3 and 4 from Eastman, N. J., "William's Obstetrics," Ed. 10, 1950, courtesy Appleton-Century-Crofts, Inc.)

FIGURE 3. Internal podalic version. Grasping feet, both if at all possible, makes the turning much easier. Note use of long gloves.

Podalic version in the properly selected case should be both an easy and a safe procedure for both mother and child. If it should prove to be difficult to execute in a particular case, it probably was not the procedure of choice and some other method of delivery should have been selected.

Effects of Early Postoperative Ambulation

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Results of early postoperative ambulation in 1700 major surgical cases are compared with those of late postoperative ambulation in 1200 similar surgical cases. The beneficial effects of early ambulation are shown: marked decrease in the complication rate; no increase in the postoperative hernia rate; a shorter hospital stay, and a more rapid rehabilitation of the patient.

THE beneficial effects of early ambulation in postoperative patients do not appear to be fully appreciated by many physicians and surgeons in this country. This method of management of surgical patients is not an entirely new idea, having been proposed over 50 years ago by Ries.[20] Recently many favorable reports have contributed a great deal to the advancement of this sound program.[1-19]

L. T. PALUMBO

Prolonged bed rest results in many undesirable physiologic changes. These disturbances include skeletal and smooth muscle weakness and loss of tone, loss of calcium and nitrogen from the body, reduced vital capacity, decreased cardiac output, slowing of circulation, and delay in wound healing.[2-8,10,11,15-17] As a result of these changes, many complications may develop during the postoperative period. These complications may occur in the gastrointestinal tract as evidenced by ileus, constipation, flatus, nausea, vomiting and/or decrease or loss of appetite. Pulmonary complications, such as pneumonia and atelectasis, are usually due to poor pulmonary ventilation, decreased pulmonary circulation, retention of bronchoalveolar secretions secondary to depression of cough reflex and inhibition of the thoracic and abdominal muscles due to pain. The slowing of peripheral circulation predisposes to thrombophlebitis and phlebothrombosis which may result in pulmonary embolism or infarction. The delay in wound healing may result in wound disruption or evisceration and may lead to a greater incidence of postoperative hernia.

This survey was conducted for a four year period ending in 1950. For the first two years it was the policy of our service to ambulate surgical patients after the sixth postoperative day. After 1948 the great majority of the patients were ambulated before the third day. Since that time a study has been made of the 2 groups of patients upon whom major surgery was performed; in 1 group were 1700 (58.5 per cent) patients ambulated early and in the other, 1,203 (41.5 per cent) who were ambulated late.

Early ambulation consisted of arising from bed, standing, walking and sitting either in a chair or on the side of the bed on the first or

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second postoperative day. The majority of patients in this group were ambulatory on the first day. These activities were carried out in conjunction with the department of physical medicine, which supervised and assisted these patients, two to three times daily until each patient was able to manage safely by himself. The patients placed in the late group were ambulated after the sixth postoperative day, the majority between the seventh and fourteenth days. In both groups deep breathing and leg exercises were instituted immediately after the patient recovered from anesthesia. These activities were carried out several times daily for a specific period of time to meet the requirements of each special group of patients.

The surgical procedures surveyed in both groups are shown in Table 1. The greatest number were hernioplasties (49.7 per cent), appendectomies (26.6 per cent), sympathectomies (6.3 per cent), biliary tract surgery (5.1 per cent) and gastrectomies (3.7 per cent).

The average age was 43.3 years for the early group and 43.1 years for the late group. In each specific operative group the average age was about equal. All of the patients were males.

Results

In the combined series there were 182 (6.2 per cent) complications, including those of the wound. In the early ambulatory group, excluding wound infections and hematomas, there were 40 (2.3 per cent) complications and in the late group 69 (5.7 per cent). The most frequent complications were pulmonary and gastrointestinal in type.

The incidence of pulmonary complications in the early group was 31 (1.2 per cent) and in the late group 32 (2.6 per cent). Atelectasis and/or pneumonia occurred in 19 (1.1 per cent) patients and pulmonary embolism in 2 (0.1 per cent) patients in the early ambulatory group. In the late ambulatory group atelectasis and/or pneumonia developed in 29 (2.3 per cent) patients and pulmonary embolism in 4 (0.3 per cent). Pulmonary complications occurred more frequently in those patients who had had pulmonary surgery or a surgical approach through the thoracic cavity; the incidence of complications was about twice as frequent in the late ambulatory group (22 per cent) as compared with the early group (12 per cent).

TABLE 1

EFFECTS OF EARLY AND LATE POSTOPERATIVE AMBULATION IN 2,903 CASES

(TYPES OF SURGICAL PROCEDURES INCLUDED IN THIS STUDY)

SURGICAL PROCEDURE	NUMBER OF CASES	
	Early Ambulation	*Late Ambulation*
Appendectomy	698	131
Biliary tract operations (cholecystectomy and common duct)	109	36
Gastrectomy, partial	45	63
Hernioplasty—inguinal, epigastric, femoral, umbilical and ventral	572	861
Lobectomy, pulmonary	21	5
Nephrectomy	16	18
Sympathectomy—lumbar, dorsal and thoracolumbar	142	53
Thoracotomy	25	20
Thyroidectomy, partial	48	4
Ulcer, peptic—closure of perforation	24	12
TOTALS	1700 (58.5 per cent)	1,203 (41.5 per cent)

TABLE 2

COMPARATIVE STUDY OF SURGICAL MORTALITY IN EARLY AND LATE POSTOPERATIVE AMBULATION

CAUSE OF DEATH	OPERATION PERFORMED	AMBULATION			
		Early (1700)		Late (1,203)	
		Number	*Per Cent*	*Number*	*Per Cent*
Atelectasis, massive, bilateral	Appendectomy	1	0.14		
Atelectasis, massive, and tension pneumothorax	Thoracotomy			2	10.0
Cardiac failure	Thoracotomy			1	5.0
Coronary occlusion	Appendectomy	1	0.14		
	Cholecystectomy	1	0.91		
	Sympathectomy, lumbar	1	0.83		
Mediastinitis	Thoracotomy			1	5.0
Peritonitis, acute	Cholecystectomy	1	0.91		
	Gastrectomy, partial	1	2.2	1	1.5
Pulmonary embolism and edema	Gastrectomy, partial			1	1.5
TOTALS		6	0.35	6	0.49

Ileus developed in 13 (0.07 per cent) of the early group as compared to 21 (0.17 per cent) in the late group. It occurred more frequently in those patients who had appendectomies, biliary tract surgery, nephrectomies and sympathectomies.

Acute thrombophlebitis occurred infrequently in both groups; the incidence was 0.3 per cent in the early group and 0.6 per cent in the late group. This complication developed more frequently in those patients who had pulmonary surgery or surgery through a thoracic wound.

Catheterization was required much less frequently in the early group, being necessary in 1.3 per cent of this group as compared to 3.9 per cent in the late group.

Wound complications were infrequent in both series. Practically all abdominal incisions were transverse or oblique muscle splitting in type. The majority of wounds were closed with nonabsorbable sutures, most frequently with silk. Only one wound disruption occurred in 2,903 operations; this occurred following a nephrectomy. Partial separation of the wound developed in 7 patients, 2 (0.11 per cent) in the early group and 5 (0.4 per cent) in the late group. Wound infections and hematomas occurred with equal frequency in both groups. There appeared to be no delay in wound healing in the group ambulated early. The patients ambulated early experienced less discomfort and generally required less sedation, both in frequency and in size of dose for the relief of pain.

The incidence of postoperative hernias was not increased as a result of early ambulation as shown in two of our separate and definitive follow-up studies.[18,19] In 340 primary inguinal hernioplasty patients followed for two to four years who ambulated late, the recurrence rate was 1.38 per cent as compared with 202 ambulated early with a recurrence of 1.48 per cent. In 119 patients who had biliary tract surgery 4 developed hernias. Two (2.1 per cent) occurred in 91 patients who had a right oblique subcostal muscle-splitting incision. All of these patients were ambulated early. In 28 patients an upper right midrectus incision was employed. This latter group was ambulated late, with a hernia incidence of 7.1 per cent.

The period of hospitalization was reduced in the majority of separate surgical groups studied. The greatest reduction occurred for biliary tract surgery, hernioplasty, nephrec-

tomy, lumbar sympathectomy, and thyroidectomy. The average hospital stay was 14.4 days for the early ambulatory group as compared with 19.2 days for the late group. This represented a saving of 7,960 days for the patients in the early ambulatory group.

There were 12 (0.41 per cent) surgical hospital deaths in this survey of 2,903 patients. Six (0.35 per cent) occurred in the early ambulatory group; 1 was due to massive bilateral atelectasis, 3 to coronary occlusion, and 2 were due to generalized peritonitis. In the late group 6 (0.49 per cent) deaths occurred; 1 patient died from pulmonary embolism and edema, 1 from generalized peritonitis, 1 from cardiac failure, 1 from mediastinitis, and 2 from massive atelectasis and tension pneumothorax (Table 2).

Summary and Conclusions

The effects of early postoperative ambulation in 1700 male patients were compared with the effects of late ambulation in 1,203 male patients. This survey covered a four year period during which time late ambulation was the policy from 1946 to 1948 and early ambulation was the routine established thereafter. Most of the patients in the early ambulatory group were ambulated within the first 24 hours, and those in the late group were ambulated after the sixth postoperative day.

This study revealed that all complications, including those of the wound, pulmonary, gastrointestinal and urinary tracts occurred at least twice as frequently in the group of patients ambulated late.

Early ambulation did not increase the incidence of wound complications and had no deleterious effect on wound healing as evidenced by no increase in the postoperative hernia rate.

The immediate postoperative mortality was not increased as a result of early ambulation.

It appears from this survey that early ambulation was beneficial to this group of patients in decreasing the complication rates, effecting a shorter hospital stay, providing a more rapid rehabilitation of the patient and producing a great economic saving to the patient and to the hospital.

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Grateful acknowledgment is made to the Department of Physical Medicine for its cooperation and active participation in this program.

Serum Neuritis: 20 Cases Following Use of Antitetanic Serum

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Antitetanic serum is an important prophylactic and therapeutic agent. Serum neuritis should be recognized in the course of serum sickness. A review of 20 of the author's cases of this condition is presented. This complication of the use of antitetanic serum should not discourage its use.

No medical term is so overworked and misused as "neuritis." The diagnosis frequently is made by the patient or offered by the practitioner as a mental solace when no definite cause of pain can be discovered.

J. L. GARVEY

Cases of neuritis vary considerably, depending on whether the fiber of the lower motor neuron or the fiber of the posterior root is involved. A lower motor neuron type of lesion is characterized by a flaccid or flail type of paralysis with muscular atrophy and, in certain groups in which the anterior horn cell degenerates slowly, muscle fasciculation. By and large, muscle fasciculations are uncommon in localized neuritis.

Lesions vary in site and in degree of motor or sensory and at times atrophic disturbances. In addition to the flaccid type of paralysis with muscular atrophy, a characteristic finding is a diminution or loss of the deep tendon reflexes and the skin reflexes. The deep tendon reflexes are more frequently affected than those of the skin. The statement has been made that in the early irritative stage of multiple neuritis or neuritis, the tendon reflexes are increased; I do not think that this is wholly true.

Neuritis, both general and local, usually is easily recognized, but too often an etiologic diagnosis is not established. Textbooks list innumerable causes for polyneuritis. In my opinion the simplest and most useful classification would be to use the general headings of virus, bacteriotoxic, deficiency or metabolic and chemical. In addition, trauma may be a factor in localized neuritis.

The term "neuritis" is used to describe any process involving the peripheral neuron and causing a functional loss which, depending on the anatomic area involved, may be sensory, motor or mixed. It seems unnecessary to introduce other terms such as neuronitis, for usually when the axon is primarily affected there is soon a change in the nerve cell and vice versa.

The prophylactic and therapeutic use of various serums is common enough to justify a discussion of this condition and a report on my experience with a disabling type of neuritis associated with anaphylaxis and serum sickness following the use of antitetanic serum. While serum neuritis may be

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

caused by diphtheria antitoxin, scarlet fever antitoxin, antipneumococcus serum, etc., tetanus antitoxin heads the list of serums producing this condition. According to Bennett,[1] approximately 115 cases had been reported prior to 1939. Other papers describing serum neuritis have appeared in the literature since then. Woolling and Rushton[2] of the Mayo Clinic recently reported on 2 typical cases encountered within a period of one month.

In 1938 I examined a previously healthy man who had been given 1500 units of antitetanic serum for prophylaxis when his right foot was peppered with about 80 porcupine quills. Nine days later there was severe pain in his right shoulder and marked spasm in the muscles of the neck and shoulder girdle, necessitating hospitalization. The attending physician, believing that he might have tetanus, gave him additional antitetanic serum. He became gravely ill as the result of serum sickness. Gradually the pain and tenderness subsided, and it was then noted that he had a marked weakness about the shoulder girdle. The weakness on the left side promptly improved.

When I saw the patient, he still had marked weakness on elevation of the right arm, the bony landmarks about the shoulder were more prominent on the right side than on the left, he had a sensation of tingling in the arm, there were occasional fibrillary tremors in the region of the left deltoid muscle, and diminished superficial sensation was noted in a small area over the right deltoid area. To the best of my recollection, this was the first case of serum neuritis that I had occasion to recognize.

I was reminded that prior to this I had seen patients who presented a similar clinical picture of neuritis about the shoulder girdle, cases in which the etiology was obscure. As a result of this experience, I interested myself in all unexplained cases of local and generalized neuritis and, as a result, have observed 20 cases which I regard as unquestionable examples of antitetanic serum neuritis.

The following case represents one of the pitfalls in early recognition of the condition. A young college student was working in a veneer plant during his summer vacation. On July 29, 1942, while lifting a heavy wooden door, he suddenly experienced a "catch-like" pain in the left shoulder. Following this he noticed increasingly severe pain in his right shoulder. He became ill and went home. He attributed the general ill feeling to the severity of the pain. He remained in bed for several days, at the end of which time he was aware of the fact that he had a right wrist drop. He was seen by a number of physicians and had a complete examination in a well known clinic. Several months later various examiners reluctantly concluded that the wrist drop probably was the result of violent muscular compression of the musculospiral nerve caused by the lifting of the door. A claim for workmen's compensation was made.

The disability persisted, and two years later I was asked to see him relative to the prognosis for recovery. I was not impressed by the explanation for the wrist drop inasmuch as recovery had not taken place. Then, as a result of direct inquiry concerning the use of antitetanic serum, he told me that nine days prior to the general ill feeling and the severe pain in the left shoulder and arm he had been given antitetanic serum by a plant nurse for a puncture wound of the right hand. At no time had he been questioned regarding antitetanic serum, and the incident had not seemed significant to him.

Trivial injuries and prophylaxis with antitetanic serum are often forgotten by patients, and unless the physician is acquainted with the condition when an unexplained neuritis presents itself, the diagnosis will not be established.

Of this group of patients that I have seen, only one came to me with a diagnosis. A healthy young candidate for a varsity football squad received a laceration of the upper lip while playing football. He was given 1500 units of antitetanic serum in the left deltoid region. Mild axillary adenitis was noted six days later. Nine days later he complained of severe pain in both shoulders and other symptoms of serum sickness. Numbness of the dorsum of the left hand and weakness of the wrist appeared the following day. A com-

petent neurologist of the school medical faculty promptly recognized the condition as serum neuritis involving the musculospiral nerve. Improvement started about eight months after the onset of the trouble, and by 14 months complete recovery had taken place.

While the commonest site for this radicular lower motor neuron dysfunction is the shoulder, other sites may be involved or the condition may be generalized. Five patients in this series were thus affected. One case was complicated by the therapeutic use of penicillin coincidental with the prophylactic use of antitetanic serum.

A 44 year old man presented a multiple neuritis syndrome, characterized by flaccid paralysis of the arms and legs with muscular atrophy and fasciculations. The deep tendon reflexes were abolished and sensory changes were exceedingly minimal. Early in his illness little attention was paid to the fact that he had been given 1500 units of antitetanic serum at the time of a trivial injury to the left index finger. This injury had occurred while he was at work. Further, he developed serum sickness for which ADRENALIN® was given, with relief of the symptoms of serum sickness. Promptly, weakness was noted in the legs and arms. His employer, regarding him as "lazy," discharged him. For two and one-half years this patient was denied proper care, treatment and consideration under the Workmen's Compensation Act.

In another case of interest, the patient had extensive generalized involvement and made a complete recovery in three months. Marked anaphylactic reaction occurred the day after he was given antitetanic serum as prophylaxis for a nail puncture wound of the foot. One week later he developed "joint" pains, extreme weakness and delirium. This was followed by profound weakness of the arms and legs, with vague sensory disturbances in the hands. The paralysis was of the flaccid type with loss of the deep tendon and skin reflexes.

These polyneuritic cases are interesting in connection with the case reported by Kamman and Weisberg.[3] Their patient received 1500 units of antitetanic serum subcutaneously following a puncture wound of the sole of the right foot. Hives and other characteristic symptoms and signs of serum sickness developed. A polyneuritis syndrome with facial diplegia followed. Spinal fluid contained 155 mg. of protein per hundred cubic centimeters.

A 61 year old gardener received antitetanic serum for a puncture wound. About 10 days later a severe serum reaction developed, with aching muscles, progressive flaccid weakness of the arms and legs, and mild bulbar symptoms. The amount of total protein in the spinal fluid was 50 mg. per hundred cubic centimeters, and there was no increase in cells or evidence of spinal block. His general condition within the next few days became progressively worse and death ensued due to respiratory failure. This is the only case with which I am acquainted where death occurred as the result of the rapidly progressive course of the paralysis.

Csermely[4] recently reported the first verified instance of leukoencephalomyelitis following administration of tetanus antitoxin. The histologic picture corresponded to that of para-infectious or postvaccinal leukoencephalitis. His patient was a 35 year old man in whom generalized urticaria developed on the third day after injection of 1500 I.U. of tetanus antitoxin. Symptoms and signs of a cerebrospinal process followed, and death occurred on the fourteenth day after administration of serum. It was concluded that the clinical pattern and histologic changes proved that the process was of allergic nature.

In connection with serum sickness and leukoencephalitis, I would call attention to 2 cases in my series in which encephalitic features overshadowed the neuritic involvement. A middle-aged woman received a puncture wound and was given antitetanic serum. The classic symptoms of serum sickness developed. In addition, she became grossly confused and agitated, and had ocular palsies. About 11 days after the onset of the serum sickness the cerebral manifestations subsided and it was noted that she had a neuritis of the left arm. The paralysis was of the flaccid type. Within six weeks this phase of the condition also cleared up.

I have had occasion to see 3 additional

patients who developed mild allergic phenomena and localized neuritis, in 1 instance following the use of anti-streptococcic serum, and in 2 cases following the use of penicillin. In each instance the character of the neuritic involvement was indistinguishable from that seen in the classic cases of serum neuritis following the use of antitetanic serum.

The anatomic distribution of neuritis in my group of 20 cases is shown in Table 1.

TABLE 1

ANATOMIC DISTRIBUTION OF NEURITIS IN 20 CASES OF SERUM NEURITIS

DISTRIBUTION	NUMBER OF CASES
General	6
Both shoulders	2
Right shoulder	5
Left shoulder	3
Left ankle	1
Musculospiral nerve	2
Ulnar nerve	1
	20

The youngest patient in this group was 18 years of age and the oldest 61 years of age. Eighteen were men and 2 were women. Eight patients had symptoms of severe serum sickness, 10 of moderately severe and 2 of mild. In 2 cases there were associated cerebral manifestations.

Neuritis associated with serum sickness should be strongly suspected if severe localized or general radicular pain appears early in the course. Usually this pain is so severe that any early paralytic features are masked. Because of this feature, detection of the paralysis is usually delayed for weeks or months. The flaccid atrophic paralysis appears in the neural segments represented by the pain distribution. Striking sensory deficit is uncommon, as are muscle fasciculations.

My experience throws little light on the pathogenesis of the condition. Woolling and Rushton[2] state that the most plausible theory is that of urticarial edema of the perineural tissue, with consequent production of compression neuropathy.

Nash, Bryant and Coller[5] state in connection with the presentation of their experience with 81 cases of tetanus: "It cannot be reiterated too often that there is no substitute for the prophylactic treatment of tetanus, preferably by active immunization with the toxoid or certainly by the adequate administration of antitoxin with any suspicious wound. If a patient has not been actively immunized, a physician cannot assume the responsibility of treating a wound that might potentially harbor and permit growth of tetanus bacilli, unless he administers antitoxin."

In spite of this disabling type of neuritis associated with the use of antitetanic serum, I wish to emphasize that it should not alter the prophylaxis and treatment of tetanus. Until the civilian population is actively immunized, the hazards of a disease of this type will not be reduced. All patients in my series were from the civilian population.

Many patients with mild cases probably recover without knowing that neuritis has complicated the serum sickness. It is my impression and that of most authors that some form of permanent disability results in about 20 per cent.

A long period of time may elapse before healing takes place. I have observed patients in whom complete recovery occurred after 24 months.

Pitfalls in diagnosis are (1) no history of injury or use of serum; (2) very mild symptoms of serum sickness; (3) failure to recognize the significance of severe pain during serum sickness.

Delay in recognition of the condition may delay therapy. The treatment for the neuritis in the early stage is the same as that for serum sickness in general. The medicolegal rights of the patient may be jeopardized. It is rather difficult at times to justify the relationship of this condition to a trivial injury.

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Early Recognition of Bronchogenic Carcinoma

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Bronchogenic carcinoma is increasing more than any other cancer in the body. The unprecedented increase is probably due to the carcinogenic effect of cigarette smoking. Unfortunately, a long delay usually occurs between the onset of the disease and the diagnosis. All men past 40 years of age who have been heavy smokers should have x-rays of their chest every three to six months in order that bronchogenic cancer can be detected early.

ALTON OCHSNER

THE mortality rate for bronchogenic carcinoma is increasing more rapidly than that for any other form of cancer (Figure 1). If the incidence of this disease continues to increase at its present rate, more than 47,000 persons in the United States will have cancer of the lung in 1970 (Figure 2). In 1920, 1.1 per cent of all cases of cancer were primary lesions of the bronchi; in 1930 this figure was 2.2 per cent, and in 1948 it was 8.3 per cent. Based on the present day increase we predict that by 1970 the figure will be 18 per cent—almost 1 in 5 (Figure 3).

There is a great deal of conjecture concerning the reasons for this increased incidence. We believe it is due to the carcinogenic effect of cigaret smoking. Note in Figure 4 the definite parallelism between the increase in cigaret sales and the increase in incidence of cancer of the lung.

Although women today smoke almost as many cigarets as do men, I do not think carcinoma of the lung will ever be as common in women as it is in men. Ninety per cent of cases occur in men.

Histologic Types

Incidence according to type—Bronchogenic carcinoma can be divided into three types: (1) epidermoid, (2) undifferentiated and (3) adenocarcinomatous. More than half the cases are of the epidermoid type, which occurs principally in men (Figure 5). These are the lesions which probably are the result of the carcinogenic effect of tobacco. The adenocarcinomas represent a relatively small group, a little less than 20 per cent, and are more frequent in women. We believe they are the result of a congenital rest, the so-called bronchial adenoma which undergoes malignant change, and that they are not due to the carcinogenic effect of tobacco.

Incidence according to sex—Bronchogenic carcinoma is much more common in men. Of the men in our series, 57 per cent had epidermoid carcinoma, 28 had undifferentiated type and 15 per cent had adenocarcinoma (Figure 6). In women, 22 per cent of the

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

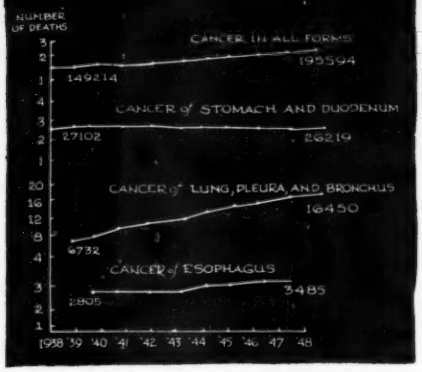


FIGURE 1 *(above)*. Mortality rate for bronchogenic carcinoma in the United States.

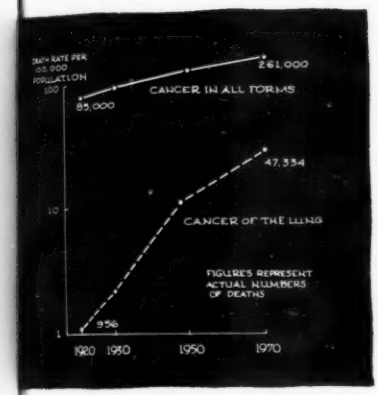


FIGURE 2 *(left)*. Estimated incidence of bronchogenic carcinoma in 1970 if present increase continues.

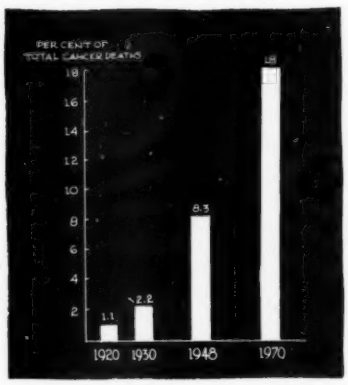


FIGURE 3. Estimated number of deaths from bronchogenic carcinoma in 1970 if present increase in mortality rate continues.

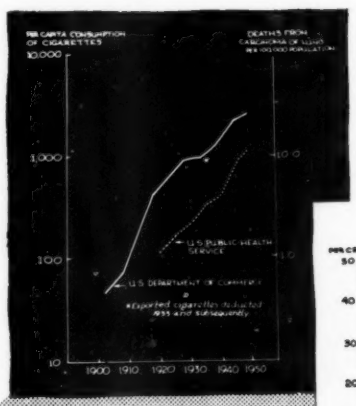


FIGURE 4. Parallelism between increase in cigaret sales and increase in incidence of cancer of the lung.

lesions were epidermoid, 28 per cent undifferentiated and 50 per cent adenocarcinoma.

Incidence according to age—The greatest number of cases occur in the fifth, sixth and seventh decades of life (Figure 7). The two extremes of life are not exempt, but cancer of the lung is the one form of carcinoma whose incidence does not increase with advancing age. There is an increase up to about the sixty-fifth year and then it tends to decrease. A probable reason for this is that in individuals who are susceptible to the effects of tobacco, cardiovascular lesions develop and these persons do not live long enough for cancer to develop in their older age.

Epidermoid carcinoma becomes more likely with advancing age, and adenocarcinoma less so. We think this is due to the fact that as one grows older, the effects of the carcinogen have had a chance to exert themselves, whereas adenocarcinoma, being on the basis of a congenital rest, is much more likely to develop at an earlier age (Figure 8).

Anatomic Location

Bronchogenic carcinoma occurs with about equal frequency in both lungs (Figure 9).

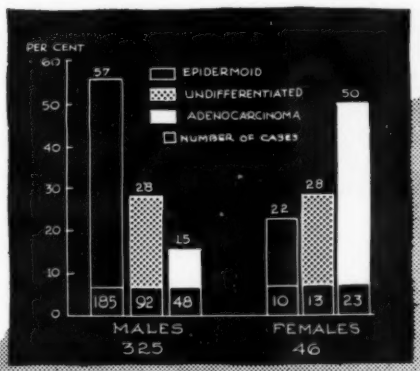
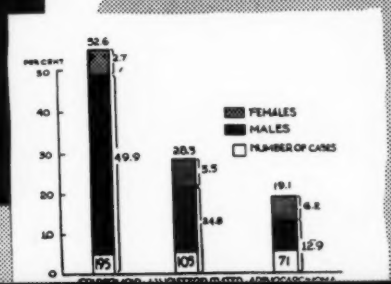


FIGURE 5 *(below)*. Incidence of histologic types of bronchogenic carcinoma, 371 resected cases.

FIGURE 6 *(right)*. Incidence of histologic types according to sex, 371 resections.



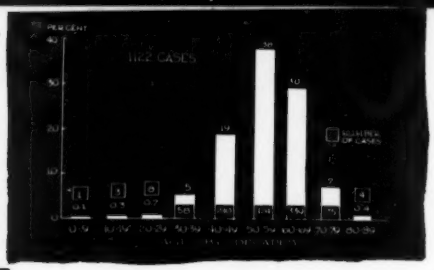


FIGURE 7 *(above)*. Incidence of bronchogenic carcinoma according to age, 1,122 cases.

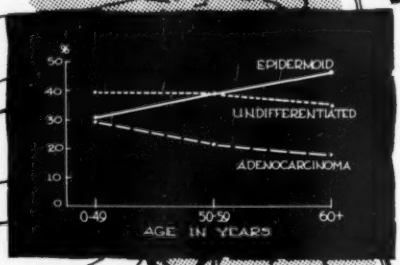


FIGURE 8 *(left)*. Breakdown of histologic types according to age.

In our series the right lung was affected in a little over half the cases. The important point in regard to location is that the lesions affected primarily the upper lobes, and these may not be visible on bronchoscopic examination. I emphasize this because a negative bronchoscopic examination in no way rules out a bronchogenic lesion.

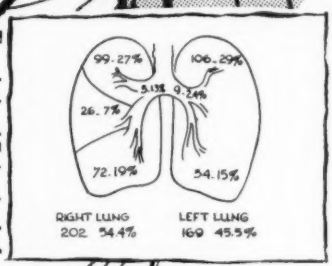


FIGURE 9 *(above)*. Anatomic location of lesion, 371 resected cases.

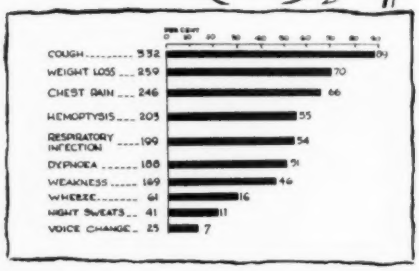


FIGURE 10 *(left)*. Symptoms on admission, 372 cases of bronchogenic carcinoma.

Symptoms

The diagnosis of bronchogenic carcinoma should be made before symptoms appear, and I will say more on that later. The clinical manifestations begin insidiously. Over half of our patients gave a history of a respiratory tract infection, and unfortunately such histories are very common today. Five years ago considerable emphasis was placed on the importance of viral infections of the lung, and though there undoubtedly is such a thing as viral pneumonitis I think we should be extremely cautious in making such a diagnosis in a man past 45 years of age who has been a heavy smoker. It is true that he may have a viral infection, but there is a considerable chance that he has bronchogenic carcinoma. If a man in his forties has a respiratory tract

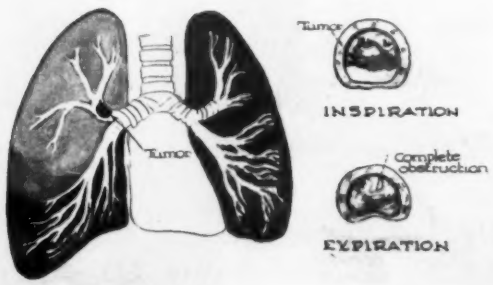
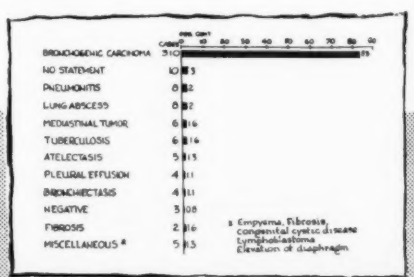


FIGURE 11. Obstructive emphysema.

FIGURE 12. Findings on roentgenologic diagnosis, 371 resected cases of bronchogenic carcinoma.



infection which does not respond to treatment in a relatively short period of time, the possibility of bronchogenic carcinoma should be suspected.

Cough was the symptom most commonly encountered in our 372 cases (Figure 10). All individuals who smoke have a cough—so-called smoker's cough.

Hemoptysis should never be disregarded. It means ulceration, and in an individual more than 40 years of age who previously had no difficulty it usually means carcinoma.

Thoracic discomfort also is a significant finding. Wheezing in a person who does not have asthma means bronchial obstruction and must be investigated.

Late manifestations are those of advanced disease and not those of the cancer itself: fever due to breakdown of the tumor or to the pneumonitis distal to the tumor as the result of obstruction, pain due to involvement of the parietes and of the peripheral nerve, digestive disturbances following involvement of the vagus nerves, and emaciation due to extension of the tumor.

Figure 10 lists the common symptoms and their order of frequency. I would like to call attention to the last-named symptom on this list, namely, voice change. Most thoracic surgeons believe that involvement of the recurrent laryngeal or phrenic nerves is an indication of inoperability. Obviously this means extension beyond the lung, but it does not mean the lesion is not resectable. Only after the chest is opened can one determine the lesion's operability. In 7 per cent of our cases there was preoperative evidence of recurrent laryngeal paralysis, and yet we were able to resect the lesions. Not all these patients are well, but 2 have been well for more than five years since operation.

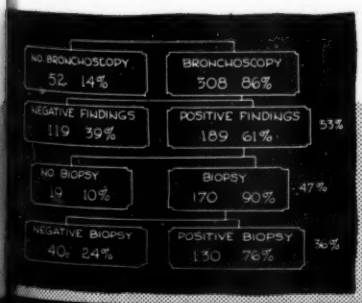
Diagnostic Methods

The diagnosis of bronchogenic carcinoma is not difficult if its possibility is kept in mind. The best diagnostic procedure is roentgenography. I would like to urge that all persons past the age of 40 years who are heavy smokers have a chest roentgenogram at least every six months and preferably every three months. A roentgenogram can disclose a shadow by virtue of infiltration of the parenchyma about the tumor, or an early manifestation such as obstructive emphysema. The bronchus is not a rigid tube; it dilates during inspiration and contracts during expiration. A tumor which incompletely fills the bronchus during inspiration permits air to get beyond the tumor because of the dilatation of the bronchus; during expiration, with contraction of the bronchus, the air is trapped distal to the tumor, and obstructive emphysema results (Figure 11).

Atelectasis as a result of obstruction of the bronchus with obstruction distally in a man past 40 years of age means bronchogenic carcinoma.

Bronchography is of value particularly in cases in which the lesions involve the upper lobes or are situated down in the periphery. Bronchoscopy, though a valuable method, fails to disclose the lesion in about two-thirds of cases because they are beyond the bronchoscopic vision or around the corner.

Cytologic examination of bronchial secretions is the best method of making a positive diagnosis preoperatively. The cytologist must not only be a pathologist who knows tissue



URE 13. Results of bronchoscopic examination, 360 resected cases.

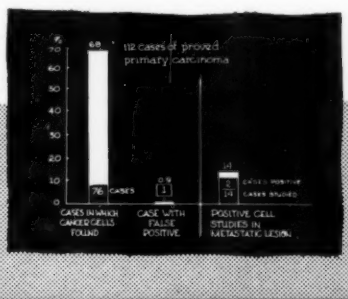


FIGURE 14. Results of cytologic examination, 290 cases of bronchogenic carcinoma (November 1, 1948 to January 31, 1951).

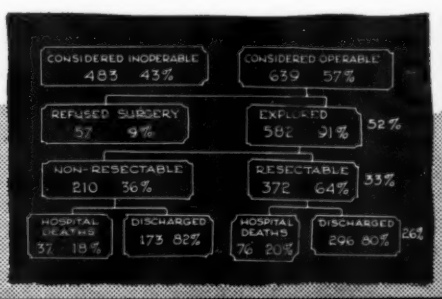


FIGURE 15. Summary of 1,122 cases of bronchogenic carcinoma.

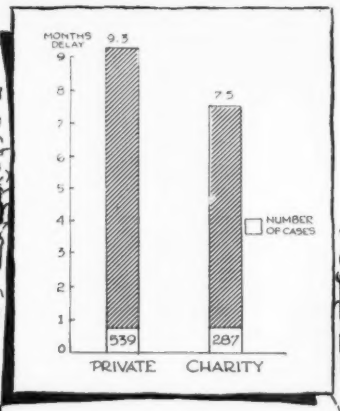


FIGURE 17 *(above)*. Comparison of delay between symptoms and diagnosis in private and in charity cases.

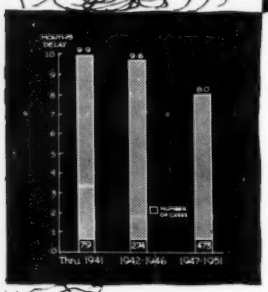
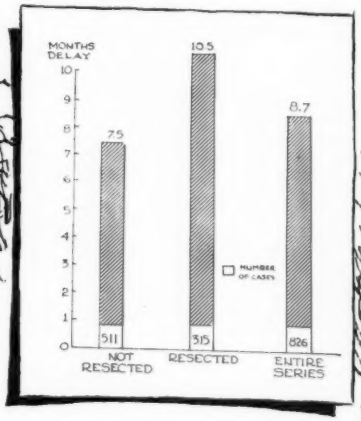


FIGURE 16 *(left)*. Length of time which elapsed between onset of symptoms and diagnosis of bronchogenic carcinoma.

FIGURE 18. Delay before definitive treatment was instituted, resected and non-resected cases.



diagnosis but also know cytologic diagnosis and be willing to spend hours looking at multiple specimens. If a good cytologist is available, the diagnosis can be made in 70 per cent of cases.

A good deal of controversy has arisen as to which is more valuable, examination of sputum or examination of bronchial secretions. Specimen for specimen, examination of aspirated secretions is more valuable, but because one can make many examinations of sputum whereas one does relatively few bronchoscopic examinations, the sputum examinations give more correct diagnoses.

Thoracoscopy, though not of much diagnostic importance, is an important procedure for prognostic purposes. Thoracoscopic examination is of value in determining extension to the pleura, for instance.

Aspiration biopsy is mentioned here only to be condemned. Although valuable in diagnosis, it is hazardous if one wants to offer a patient something with regard to cure. We have seen 4 patients for whom aspiration biopsy was done and in whom there was implantation in the chest wall as a result of the tumor cells being carried out with the aspirating needle. We do aspiration biopsies only in patients who have hopelessly inoperable lesions and in whom we want conclusive diagnostic proof.

We were able to make a positive diagnosis of bronchogenic carcinoma in only 80 per cent of our cases before the chest was opened. Thoracic exploration is justified in a person, particularly a man over 40, who has unexplained thoracic discomfort and when the possibility of a bronchogenic neoplasm cannot be excluded.

Positive roentgenologic diagnosis was obtained in 83 per cent of our cases (Figure 12). In a little more than one-third of the cases, bronchoscopic examination resulted in a positive diagnosis (Figure 13). By cytologic examination of the sputum, however, positive diagnoses were obtained in approximately 70 per cent of cases (Figure 14).

Treatment

We believe the only type of therapy is pneumonectomy. I think it is just as irrational to consider a lobectomy in a case of bronchogenic carcinoma as it would be to do a quadrant resection of the breast in a case of breast

carcinoma. Only by removing the entire lung and the mediastinal lymph nodes can one possibly obtain a cure. We do some lobectomies, but only if it has been shown by pulmonary function studies that the patient will not tolerate a pneumonectomy.

The results in 1,122 cases of bronchogenic carcinoma are shown in Figure 15, and it is not a good report. Forty-three per cent of the patients had inoperable lesions when first seen. In 639, or 57 per cent, the lesions were thought to be operable, and 9 per cent of these patients refused surgery. Exploration was done in 582 cases, of which 36 per cent were found to be nonresectable lesions; 18 per cent of these patients died in the hospital. Resection was done in 372, 33 per cent of the entire group. Of these, 296 patients (80 per cent) left the hospital—26 per cent of the entire group.

Delay in Diagnosis and in Treatment

We recently attempted to determine what is responsible for the delay in diagnosis, and Figure 16 illustrates that the length of time before diagnosis is made has decreased. Breaking this down into the two types of cases, private and charity (Figure 17), we learned that for private patients the delay was longer than for charity patients—an average delay of 9.3 months in private cases compared with 7.5 months in charity cases.

Another astonishing finding was the delay from the onset of the first symptoms to the time when definitive therapy was instituted (Figure 18). In cases in which resection was not done, this period was 7.5 months; in cases in which resection was done, it was 10.5 months. In other words, in patients in whom we were able to resect the lesions the delay before therapy was about three months longer. This sounds paradoxic, but it means simply that in the patients in whom we were able to do resection we found the slower growing tumors and therefore they could be resected

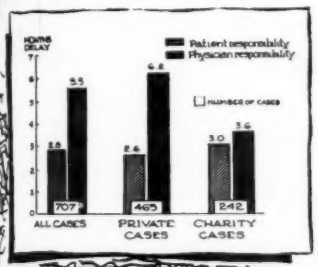


FIGURE 19. Comparison of the patient responsibility and physician responsibility for delay in treatment.

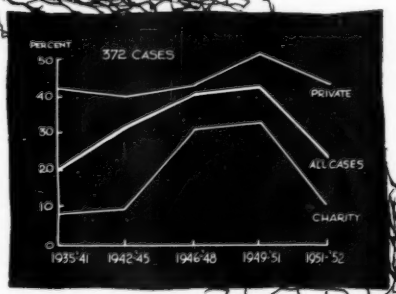


FIGURE 20. Comparison of incidence of resection by periods, 372 cases.

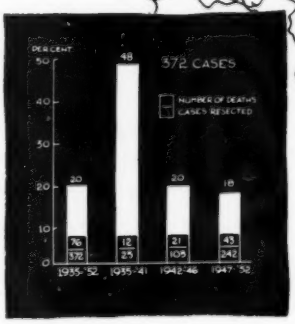


FIGURE 21. Hospital mortality rate, 372 resected cases.

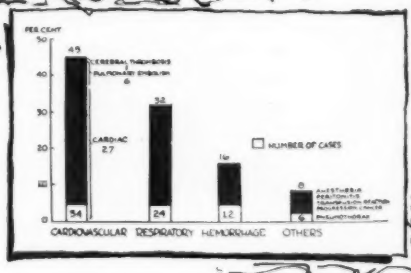


FIGURE 22. Causes of hospital deaths, 372 resected cases (76 deaths).

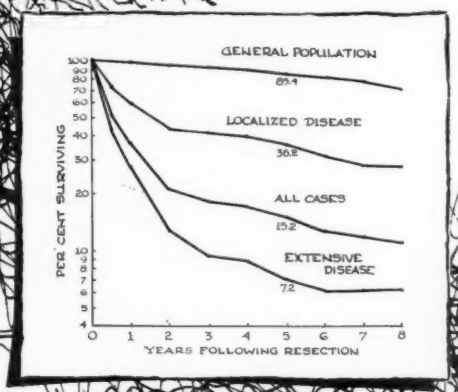


FIGURE 23. Survivals, resected cases.

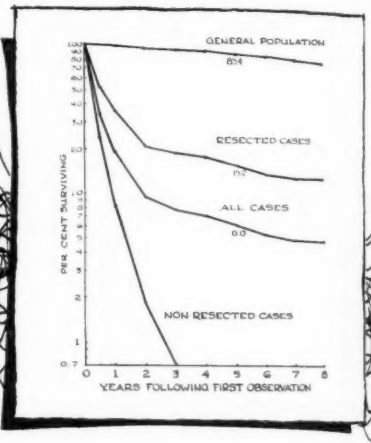


FIGURE 24. Survivals, comparison between resected and nonresected cases.

even though there was a longer delay.

A disturbing point is illustrated in Figure 19, a comparison of the cases in which the delay was the physician's and those in which it was the patient's. For the entire group, the patient delay was 2.8 months, the physician delay 5.5 months. This discrepancy is even greater for the private cases—patient delay 2.6 months, physician delay 6.2 months. The responsibility was about equally divided for the charity cases.

I think this means that the patients who were able to pay—the private cases—had a diagnosis of pneumonitis, were put in the hospital and were treated for various periods of time, whereas the indigents who were not able to pay were referred to the hospital more readily.

During the last year the delay has been longer than previously (Figure 20). I think this is because more patients are being treated as cases of viral pneumonia. About 20 years ago, when we first began doing resections in these cases, I thought we were just as justified in doing palliative resection for carcinoma of the lung as for other forms of cancer. No surgeon would hesitate to remove a stomach, even though there were metastases to the liver, to eliminate the fungating mass, so we have done it in carcinoma of the lung. Almost three-fourths of our patients had extension beyond the lung, and this fact indicates some of the necessary supplementary procedures: ligation inside the pericardium in 36 per cent; resection of the chest wall, 15 per cent; suture of the atrium, 13 per cent; resection of the diaphragm, 12 per cent, and even resection of a portion of the cava in 1 case.

The hospital mortality rate for bronchogenic carcinoma is shown in Figure 21. Figure 22 illustrates the causes of death. There were 76 deaths, most of them cardiovascular in nature, and the greatest number were cardiac. When one realizes that these patients are in the fifth and sixth decades of life, it is appreciated that there will always be an irreducible number of cardiac deaths. Eighteen per cent of the patients who underwent resection are alive after five years.

A comparison of the resected group with the nonresected group discloses a significant difference: Of 317 patients in the nonresected group, no patient lived longer than four years, and only 1 lived for that length of time (Figures 23 and 24). In the resected group 18 per cent were alive at the end of five years.

Technics in Diagnosis of the Neuroses

JOHN R. PETERS*

College of Medical Evangelists School of Medicine, Los Angeles

This presentation is a case of a typically evolving psychoneurosis showing the development of psychopathology which is first relatively simple anxiety, but which later progresses into a conversion.

Psychoneuroses are diagnosed on the same basis as other conditions, by past history, present symptoms and clinical experience of the examiner.

A REPORTER for the Columbus *Dispatch* once enrolled in a three month course at the Ohio State University in an attempt to learn the meaning of psychology. Following the quarter of study, she wrote that although she still didn't know what psychology was, she did know what a psychologist was, namely, an individual who tells you something you already know in terms you don't understand.

All of you see psychoneurotic patients, and for the most part the family physician should be able to handle them, be they major psychoses or minor psychoses or psychoneuroses. The greatest insult you can give a patient is to say, "You should see a psychiatrist," because this statement usually is made after everything else has been tried and no improvement is noted.

Psychoneurosis, neurosis and the various types of psychoneurotic reactions are all one and the same. A fairly satisfactory definition is that the psychoneuroses are a relatively benign group of personality disorders, or disturbances, representing a physiologic reaction to personal situational problems. These reactions are unconsciously motivated, shall we say, or at least out of voluntary control. The symptoms represent individual ways of meeting specific stresses.

As in other syndromes or diseases, accurate diagnosis depends on the examiner's knowledge, and the technics differ little from those used in any other condition. In general, making a diagnosis necessitates investigation and elimination. Specifically, however, a good history is more important in an investigation of a psychoneurosis than in any other disease state.

We see only that which we know, and thus nomenclature is important only as an association to which one can refer in a given case. For example, in electrocardiographic study one must know the meaning of the little curves and rises, a QRS complex, a slurring S and a T wave in order to know what is going on in the patient's heart. So it is in the diagnosis of psychoneurosis.

Because medicine in general is a growing proposition, every once in a while the nomenclature must be changed. I have learned three different nomenclatures during my experience in the field of psychiatry, and the last one is the best because it tells us something. Formerly we simply called a certain syndrome a hysteria, which didn't mean a thing; the uterus didn't wander here and there, as it

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

was once thought to do, and this concept gave us the term hysteria. The present nomenclature is based on reaction types, and the old and new classifications are shown in Table 1.

TABLE 1

OLD AND NEW NOMENCLATURE OF NEUROSES

OLD	NEW
1. Hysteria Anxiety Conversion	1. Anxiety reaction
2. Psychasthenia	2. Conversion reaction
3. Reactive depression	3. Obsessive-compulsive reaction
4. Neurasthenia	4. Depressive reaction
5. Hypochondriasis	5. Dissociative reaction
6. Anxiety states	6. Phobic reaction
7. Mixed types	7. Other types of reaction

One can get a good idea of the likelihood of a neurosis developing in a given individual by taking a longitudinal section of his life. This must begin before birth, and include findings on his parents and grandparents. Then a search must be made for events that affected his nervous system.

The list of neurotic stigmas of childhood is far too long to include all of them in this discussion. A representative group is given in Table 2. Every person has one or two or more

TABLE 2

EXAMPLES OF NEUROTIC STIGMAS OF CHILDHOOD

Fainting attacks	Thumbsucking
Nail biting or nail picking	Stammering
Temper tantrums	Slowness in walking or talking
Worry	Convulsions
Dizziness	Nightmares
Handicaps	Habit spasm
Cross-eye, harelip, limp, etc.	Tics
Sleepwalking	Fears of dark, storms, heights, crowds, animals, germs, closed places, etc.
Sulking	
Enuresis	

of these stigmas, and little attention is paid to them. If an individual has no more than four, he probably is in pretty good condition, and with less than four we can assume that a person is normal.

A multiplicity of somatic symptoms not substantiated by physical findings indicates a neurosis. A person who has had four or five major operations is suspect. A person who is tired all the time, particularly if he doesn't have anemia or fever or some constitutional disease or hasn't exercised severely, is most certainly a neurotic. Table 3 lists various neurotic traits.

TABLE 3

NEUROTIC TRAITS

Headache	Backache	Muscle ache
Globus	Twitchings	Dermographia
Hyperhidrosis	Head noises	Insomnia
Formication	Tenseness	Anxiety
Introspection	Apprehension	Palpitation
Heart consciousness	Dyspnea	Numbness
Tremors	Anorexia	Fatigue

A person who has a paralysis of an extremity or of a group of muscles and who has little or no concern for this disability has placed his anxiety on the particular paralysis or paralyzed part and therefore no longer has anxiety concerning the poorly functioning member. Such a person will come to a physician not of his own volition but because someone urged him to do so. Although he was terribly nervous before, the anxiety that was in his consciousness has gone into the ailing part and he is no longer concerned.

I would like to present a patient who was brought to us by Dr. Donald McKerracher. Mr. K. is 35 years old and was first seen in July 1949. His main complaint at present is a fear of wind and stormy weather. This fear is so intense that for several years he has taken refuge in a railroad terminal whenever there is a strong wind. To protect himself, he carries a small radio with which he follows weather reports. In addition, he makes a point always of being able to get to the terminal or some other place of refuge if it is necessary to get away from the wind.

Mr. K. came from a large family—12 children—which was dominated by a rigid, religious father whose answer to all emotional

problems was hard work. At the age of 5 years the patient almost died of pneumonia and for several months thereafter he was protected by being kept indoors and away from windows. Can you see the pattern that is being laid down? There were two recurrences of pneumonia during boyhood.

A second complaint, and the most distressing one to him, was enuresis. This continued unabated through the patient's twenty-sixth year of life. A variety of measures failed to change the symptom which made this boy different from his brothers and which isolated him socially. We call such a situation a neurotic stigma, and it was quite a stigma to this young man.

I might say that bedwetting means nothing until a child is old enough to go to school; if it ceases before the age of 6 years it is of little importance.

When the patient was 16 years old he witnessed his father's death from a coronary thrombosis. After he finished school he went to work. He was rejected by the Army because of bedwetting, and he finally consulted a doctor. At that time he was in his twenties and the physician told him he would be cured of the enuresis if he would get married. However, Mr. K. had built up taboos such as we all have, and one of these concerned going out with women and having sexual relations before he was married. This, of course, was evidence of good training, but it did contribute to the tension. Relief from the bedwetting was obtained when the patient married, as had been suggested by his physician. The patient had faith in his physician, and had only three or four bedwetting episodes thereafter.

Although the stigma of bedwetting ceased, this tremendous tension about the fear of storms and wind replaced it. Before Mr. K. married, he had no such difficulty, but within a year thereafter, a child was born. In addition, there was a tremendous fire in Cleveland and it frightened him badly. Shortly after this fire, at the age of 27 or 28, he had a brief fainting attack while looking out of a window at an approaching thunderstorm. He decided to get away from the storm and he fainted "a little bit." That incident was the beginning of his fear of wind and storm.

He failed to understand his increasing anxiety and ultimately became unemployed. He and his wife have had two children, the younger now 5 years old. A year ago his wife had three-fourths of her stomach removed because of an ulcer. Last May the patient's mother died of a stroke, and his symptoms were even more marked at that time.

Mr. K. is now so expert at following weather reports that I'll bet there are persons earning a living at weather forecasting who are not as capable.

It is interesting that he is now concerned about his stomach (following his wife's trouble), and that the symptoms are so typical of stomach disorder that young Dr. Menninger, who must be thoroughly grounded in psychoanalytic and psychiatric principles, thought there must be something wrong. To date nothing has been found, but the investigation is continuing.

More than anything else, Mr. K. would like to be rid of these tensions. He hasn't yet had a thorough study from the standpoint of the psychoanalytic approach. You will recall that I stated that most of these neuroses can be handled by the general practitioner; this patient probably represents a case in which eventually there will be a need for deeper therapy than he has had up to the present.

Recent Developments in Sickle Cell Anemia

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Sickle cell anemia is a severe and chronic disease which requires skill in management. Recent developments, mainly concerning changes in hemoglobin, are of great importance and probably will lead to better methods of treatment. These persons deserve all the help you can give them, and the results of proper management are patients who are healthier and happier despite their chronic disease.

R. D. MERCER

It is estimated that there are about 15 million Negroes in the United States and that 8 per cent, or about 1.2 million, have the sickling trait. Varying estimates of the number of persons with this trait who actually have sickle cell anemia range from 2.5 to 15 per cent—in other words, 30,000 to 180,000.

Herrick is credited with being the first to describe the disease (1910). Interestingly, as long ago as 1840 this unusual type of sickle cell was described in deer, and within recent years an epidemic was reported from Michigan in which deer were dying in the forests of sickle cell anemia.

A concise definition of sickle cell anemia is as follows: a chronic familial hemolytic anemia peculiar to the Negro race, characterized by sickle-shaped or oat-shaped erythrocytes, rheumatoid manifestations, leg ulcers, bone changes, symptoms of anemia, and attacks of acute abdominal pain.

Clinical Manifestations

Habitus—It has been stated frequently that persons with sickle cell anemia have a characteristic habitus. Actually this is simply the asthenic build of a chronically ill person. They are usually thin and shorter than average; often they have some dorsal kyphosis, usually a protuberant abdomen, a rather slanting shape to the eyes, and generally the appearance of a person who has been ill for a long time.

Eyes—The most frequent ocular manifestation of sickle cell anemia is jaundice. I think this is by far the most important cause of jaundice in Negroes. It is not particularly severe, amounting merely to an icteric tint to the sclera.

Skin—In the skin the outstanding finding is leg ulcers. These are seldom seen in patients younger than 10 or 12 years, but as these persons become older, ulcers of the legs become increasingly common. Scarring with deep pigmentation is characteristic, and when this occurs a hemolytic anemia should be considered. The scarring is not characteristic of sickle cell anemia particularly, but rather of the hemolytic process.

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

Heart—Sickle cell anemia is the one form of anemia in which changes are severe and chronic enough to lend themselves to permanent heart disturbances. These are manifested mostly by enlargement, systolic murmurs, and in some instances terminal cardiac failure.

Lungs—The lungs are involved in the process of thrombosis, an important characteristic of the disease.

Kidneys—The kidneys occasionally become infarcted, resulting in hematuria.

Spleen and liver—The spleen and liver are commonly enlarged, but for some reason in the adult patient they become smaller rather than larger. This is probably due to infarction and thrombosis of the spleen and to subsequent fibrosis, but we are not entirely certain of the authenticity of this determination.

Gallbladder—Gallstones are a frequent complication in adults as a result of continual hemolysis. This is not particularly true in children, although gallstones occasionally are observed.

Abdomen—The abdominal crises are by far the most dramatic and difficult facets of this disease. These again probably are related to thrombosis of the various vessels of the mesentery with some infarction of the bowel. However, frequently these patients undergo laparotomy because of a mistaken diagnosis, and no gross abnormality can be found. Nevertheless, symptoms may be dramatic, with intense pain and the patient in a state of shock or near shock, a rigid abdomen, an elevated white blood cell count, fever, and prostration. I do not believe the differential diagnosis between a ruptured appendix and an abdominal crisis of sickle cell anemia can be made in any other way than by looking at the blood smear; when you see the sickle cells you have the impression that the patient should not be subjected to abdominal surgery.

Central nervous system—Certain nerve changes are described. These, again, are secondary to thrombosis. There may be any type of symptom relating to thrombosis of the cerebral vessels.

FIGURE 1 *(left)*. Characteristic findings in roentgenogram of the skull of a patient with sickle cell anemia. The inner table can be seen, but the outer table cannot. Note the marked radial striations.

FIGURE 2 *(right)*. Anteroposterior view demonstrates the osteoporosis as well as the appearance of the radial striations between the two layers.

Bones—The changes in the long bones, in the cortex and the medullary cavity, are generally related to the rapid rate of production of erythroid elements with some expansion of the medullary cavity and subsequent thinning of the cortex. These findings are easily observed in the skull (Figures 1 and 2).

There also are changes related to thrombosis and fibrosis and osteoporosis of bone. One of the most interesting is infarction of the phalanges with actual destruction of the small bones. We have seen patients in whom roentgenograms, particularly of the hands, had the appearance of metastases in the phalanges and destruction of the small bones. These observations can be made when the

hands and fingers are swollen and extremely painful. These destroyed phalanges regenerate with extreme rapidity, and at the end of two or three months there is no evidence of any involvement.

A characteristic finding observed in roentgenograms of the skull is widening of the medullary cavity or widening of the diploë. The outer table of the skull is difficult to see, and marked radial striations—the appearance of hair standing on end—are apparent throughout.

There is collapse of the vertebrae related to osteoporosis, and in the hip the findings simulate Perthes' disease.

Recent Developments

Singer and others recently have emphasized that in addition to the hyperhemolytic crisis there also is an aplastic crisis. This is a somewhat new idea which is becoming increasingly important—that the aplastic crisis relates to the life span of the blood cells. Singer has shown that sickle cells have a life span of about 30 days, in contrast to the normal span of 120 days. By means of cross transfusion he has demonstrated that sickle cells will disappear in about 20 or 30 days if transfused into a normal person. If you transfuse blood from a person with the sickle cell trait, his cells act normally whether transfused into a normal person or into a patient with sickle cell anemia. Thus Singer has shown that there is a definite abnormality in the cell itself.

Gasser has pointed out that the aplastic crisis appears to follow a virus infection; evidently the bone marrow ceases to produce cells for a short period of time, perhaps 10 days. This is of no particular consequence in a normal person, since a reduction of the normal red cell count at the rate of 0.83 per cent a day for 10 days is not serious when it is taken into consideration that 120 days are required for cell destruction. In a patient with sickle cell anemia, however, whose so-called normal or constant count is about 2 million or 2.5 million, the rapid destruction of cells (30 days) and the 10 days of poor generation result in an extreme situation. Perhaps that is why these persons become so ill following relatively minor infections—in essence they are having an aplastic crisis.

Singer, Ogden and Harris all have been interested in demonstrating the changes of the sickle cell related to oxygen saturation. It can be shown that all cells which sickle (persons with the sickle cell trait as well as those with sickle cell anemia) will sickle 100 per cent if the oxygen is reduced low enough —in other words, if the hemoglobin is reduced within the cell.

Watson and her group in 1948 discussed the abnormalities of the red cells in newborn infants born to parents with known sickling traits. It was pointed out that very few cells in the newborn actually sickled or could be made to sickle, and yet as days or weeks went by these cells gradually increased in number until at the end of about three or four months 70 or 80 per cent of the cells sickled. Watson pointed out that this change is in accord with much older observations on the changes in hemoglobin. As you know, two distinct types of hemoglobin are universal at birth. One is the fetal hemoglobin, which is gradually replaced until at the end of about three months almost all the blood is made up of adult hemoglobin. Many definite physical characteristics have proved that these two types of hemoglobin are different. Watson showed that the sickling of the cells seemed to parallel the development of normal adult hemoglobin, and suggested that perhaps sickle cell anemia actually is related to production of normal hemoglobin.

Pauling in 1948 recorded some startling observations and interesting facts. He compared the hemoglobin of normal persons with that of persons with sickle cell anemia, using the Tiselius apparatus, and definitely proved there were decided differences in the electrophoretic mobility of the hemoglobin solutions. For normal persons the hemoglobin moved to the left as a negative ion, and for those with sickle cell anemia it moved to the right as a positive ion, and he showed for the first time that this actually is a disease of hemoglobin and not of the red blood cell per se, as previously had been thought. He also pointed out that it was probably related to the globin

part of the molecule, and he felt that it should be considered a true molecular disease. There are all kinds of diseases, but this was the first time anyone ever accused the molecule of being diseased, and actually I think that Pauling was right.

Perutz and Mitchison did some interesting studies on the differential solubilities of hemoglobin from normal persons and from those with sickle cell anemia. They postulated that perhaps this abnormality of the hemoglobin was related to a crystallization of the reduced hemoglobin which then produced the abnormality of the blood cell.

Pauling's reproduction of the curves taken by hemoglobin in his studies of its electrophoretic mobility reveals another interesting theory, one concerning the etiology of the syndrome. While the hemoglobin from a patient with sickle cell anemia had a definite movement of molecules to the right and the hemoglobin from a normal person one to the left, that from an individual with the sickle cell trait appeared to be a combination of the two. The division was not equal, however, and on that differential have been written a great many articles which attempt to explain why, if these persons really are the product of two persons with the sickle cell trait who are evidently heterozygous, the homozygous individuals are produced and they have sickle cell anemia. Although this is the best theory yet proffered, there still are many unexplained factors involved.

Harris conducted an interesting experiment with regard to the hemoglobin. He lysed the sickle cells, prepared a solution of the hemoglobin, and then allowed the hemoglobin to settle at the bottom of the test tube. He removed some of the hemoglobin, smeared it as one would a blood smear, and examined it. The hemoglobin itself (and this is without the stroma—this is straight hemoglobin allowed to settle) assumed the configuration of the oat-shaped cell. This seems to back up the previous observation that this may well be an actual physical change in hemoglobin within the stroma of the cell and that the cells just stretch around the abnormal hemoglobin molecules. I think Harris' observations are startling and certainly show a good way to prove a theory.

Principles of Management

The information we have on this disease does not help us much as far as treatment is concerned. I believe these persons need more than the services of a specialist or of a hematologist; I think they need a good family doctor. They need good family medicine, and understanding and cooperative parents. There must be close rapport between physician and patient if any good is to be done for them. Frequent examinations should be emphasized, the intervals between varying, of course, with the severity of the illness.

We wish to avoid as much expense as possible in managing these patients, because this is something that will continue for years and years. We check the red blood cell count and the hemoglobin periodically, but do not pay too much attention to it because these patients maintain good health with a red cell count of about 2.3 to 2.5 and a hemoglobin of about 6 to 8 gm.

We try to give transfusions before crises actually develop. A crisis frequently can be predicted. The person becomes increasingly tired, shows a little more jaundice and is just not up to par. It's difficult to put one's finger on what might be called an impending crisis, but by close observation we feel we have been able to benefit these patients and to prevent the severe abdominal crises by giving them transfusions. We are not concerned with bad effects from frequent transfusions, because we do not see how we can avoid such therapy.

Ordinary measures in management must not be overlooked. These include attention to diet, exercise and rest, and vigorous treatment of respiratory infections. Also, eradication of foci of infection is important; for example, we often advocate tonsillectomy on fairly minor indications. We try to make sure they have an adequate diet with supplements of iron. We realize this is not an iron deficiency anemia; nevertheless many patients have an additional iron deficiency and we feel that the usual iron should be given just as should the usual vitamins.

Granulomas with Tissue Eosinophilia (Eosinophilic Granulomas)

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From a complex agglomeration of data on granulomas with tissue eosinophilia have emerged two distinct and clearcut clinicopathologic entities: (1) granuloma of bone with tissue eosinophilia (eosinophilic granuloma of bone), which is accompanied by cutaneous manifestations at times, and (2) facial granuloma with tissue eosinophilia. These two disorders are described, and a brief discussion is presented of a motley group of lesions which require attention because they may simulate the aforementioned clinicopathologic entities on either or both clinical and microscopic grounds.

E. P. CAWLEY

THE interest of physicians in several branches of medicine has within recent years been focused on a unique group of diseases variously known as granulomas with tissue eosinophilia or eosinophilic granulomas. In succeeding paragraphs will be described (1) the distinctive group of granulomas of bone with tissue eosinophilia, which at times may be accompanied by cutaneous manifestations, (2) the clearcut group of facial granulomas featured by tissue eosinophilia and (3) a motley group of lesions which require attention merely because they may simulate (1) and (2) on either or both clinical and microscopic grounds.

Granuloma of Bone with Tissue Eosinophilia

Granuloma of bone with tissue eosinophilia (or eosinophilic granuloma of bone) is the mildest, Letterer-Siwe disease the severest, and Hand-Schüller-Christian disease the intermediate manifestation of an underlying basic disorder, the exact nature of which has not been determined.[1] One competent observer[2] has expressed the opinion that "a satisfactory working classification of these conditions should include the three separate clinical types of Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone, with transitional forms between eosinophilic granuloma and each of the other two diseases in this group." At least 6 cases[3] have been recorded in which granulomas of bone with tissue eosinophilia were accompanied by cutaneous manifestations as part of the process.

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FIGURE 1. On roentgenologic examination this lesion of the clavicle was suspected of being an example of granuloma of bone with tissue eosinophilia. This suspicion was verified on microscopic examination of tissue from the lesion.

Granuloma of bone with tissue eosinophilia occurs most commonly in males, and in patients less than 20 years of age.[4] Most of the lesions are located in the skull; other sites, in order of frequency, are the ribs, femur, pelvis, humerus and tibia.[4] The disease may be asymptomatic or there may be tenderness, pain and soft tissue swelling, without heat, at the site of the lesion. Systemic manifestations are usually absent.[4] The osseous lesions (Figure 1), which roentgenologically may suggest Hand-Schüller-Christian disease, Letterer-Siwe disease, cysts of bone, malignant growth or multiple myeloma, are solitary or multiple, 25 having been encountered in a single case.[1] The cutaneous manifestations of eosinophilic granuloma of bone which have been catalogued to date include (1) small yellowish papules which may coalesce and resemble seborrheic dermatitis, (2) sharply demarcated, moist, granulomatous plaques which appear to be the most characteristic cutaneous lesions on the basis of reported cases, and (3) fluctuant masses which may break down with subsequent formation of ulcers and sinus tracts.[1,3,5]

Histopathologic examination of both the osseous and the cutaneous lesions shows a loosely arranged granulomatous hyperplasia of reticuloendothelial cells and a variable number of eosinophils. Other laboratory examinations reveal little apart from a slight and inconstant eosinophilia of the peripheral blood.

Both osseous and cutaneous lesions usually respond satisfactorily to roentgen therapy.

Facial Granuloma with Tissue Eosinophilia

Numerous examples[3] of facial granulomas with tissue eosinophilia have been encountered since the first case was described in 1944.[6] The etiology is unknown.

Facial granulomas with tissue eosinophilia occur exclusively in adults, are confined to the skin of the face with rare exceptions[5] and are not associated with internal lesions. There may be one or several patches on the face, and these vary in size from small papules to plaques which may be several centimeters in diameter (Figure 2). They are round or oval in shape, soft or firm on palpation and of a tawny, reddish brown or purple hue. The lesions are asymptomatic, do not ulcerate, and persist indefinitely with few exceptions.[3] Facial granulomas with tissue eosinophilia may resemble sarcoid, lupus erythematosus, erythema elevatum diutinum or lymphoblastoma on clinical grounds.

Histopathologic examination of the fully developed cutaneous lesion of facial granuloma with eosinophilia shows an infiltrate which occupies the upper half of the dermis and is separated from the epidermis by a narrow zone of normal collagen.[5] This infiltrate is composed of a multiplicity of cell types, including lymphocytes, plasma cells, histiocytes and neutrophilic and eosinophilic polymorphonuclear leukocytes. The formula for these cellular components is not constant.

FIGURE 2. Facial granuloma with tissue eosinophilia occurring on the cheek just lateral to the nose and above the corner of the mouth. The lesion was dull red in color. Histologic features were typical. The cylindric mass between the granuloma and the nose was the sequel of a previous attempt to destroy the lesion by some form of cauterization.

The perivascular tissues may show degenerative changes.[3]

Facial granulomas with tissue eosinophilia are generally refractory to all forms of treatment and may even recur after surgical excision and grafting.[3] Cosmetic preparations may be used to mask the lesions.

The Motley Group of Lesions

The members of this motley and protean group, having in common only the presence of variable numbers of eosinophils in a granulomatus infiltrate, warrant enumeration because they may require distinction on either or both clinical and pathologic grounds from the two previously described entities, namely, granuloma of bone with tissue eosinophilia and facial granuloma with tissue eosinophilia. The following classification describes this group: (1) Various lymphoblastomas, especially Hodgkin's disease and mycosis fungoides, may be featured at times by cutaneous and visceral granulomas with tissue eosinophilia;[3] (2) occasional cutaneous granulomas which qualify as "ids" are characterized by eosinophilic periarteritis;[7] (3) Löffler's syndrome may be accompanied by cutaneous granulomas with tissue eosinophilia;[8] (4) the skin may react to the bites of arthropods (the bites of ticks, mosquitoes and chiggers have been most carefully investigated[9]) with a response which may be mistaken for the previously described cutaneous granulomas with tissue eosinophilia; (5) a foreign body granuloma of the skin may at times take on the characteristics of a cutaneous granuloma with tissue eosinophilia;[3] (6) a granulomatous lesion of the jejunum of unknown etiology and characterized by an excessive infiltration with eosinophils has recently been described.[10] The clinical features of this lesion simulated a malignant neoplasm of the jejunum; (7) several other nondescript lesions which defy accurate classification have been tentatively included in this motley group by some authors.[3, 11]

A detailed history, careful attention to clinical features of the lesions in question and pertinent laboratory examinations, especially x-ray and histopathologic studies, will usually suffice to distinguish members of this heterogeneous group from each other and from the two clearcut clinicopathologic entities, granuloma of bone with tissue eosinophilia and facial granuloma with tissue eosinophilia.

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CLINICAL STUDY

Therapy with a New Sulfonamide Triple Mixture: Sulfadiazine–Sulfamerazine–Elkosin

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The clinical use of a new sulfapyrimidine triple mixture in 127 adult patients with acute infections is reported. This mixture consists of equal amounts of elkosin, sulfamerazine and sulfadiazine. Elkosin replaces the isomer sulfamethazine, a commonly used third component. The latter is less soluble and subject to substantially higher in vivo conjugation. Therapeutic results and toxic reactions are presented in tables.

In discussing the relative merits of sulfonamide drugs as components of mixtures,[1] it was pointed out that combinations of substantially equal partial dosages of at least three sulfonamide drugs afforded adequate protection against mechanical obstruction of the kidneys in the absence of adjuvant alkali therapy. It was concluded at that time that, of the compounds available in the United States, sulfadiazine and sulfamerazine qualify for first and second place, respectively, as components of a sulfonamide mixture, while other drugs of this series deserve attention as possible additional members of a combination.

The elimination of sulfathiazole from "New and Nonofficial Remedies" of the Council on Pharmacy and Chemistry of the American Medical Association narrowed the choice of readily available sulfonamides which best met the required specifications as additional mixture components to sulfacetimide and sulfamethazine. At present "Council-accepted" triple mixtures containing either of these two drugs in addition to sulfadiazine and sulfamerazine are used extensively alone or in combination with penicillin and other antibiotics in the treatment of common bacterial infections.

Recently another sulfadiazine derivative has become available in the United States. This compound is an isomer of sulfamethazine, known under the trade name ELKOSIN®. Despite the very close chemical relationship of these two sulfapyrimidines, as apparent from Figure 1, they manifest essential differences in some of their physical properties as well as in their toxicity and fate in the body of an experimental animal.

Elkosin was first investigated by Meier, Allemann and Meyenburg[2] and since has been widely used in human therapy for the treatment of systemic and urinary infections, especially in Switzerland.[3] More recently American investigators have confirmed the clinical value and low toxicity of this sulfonamide compound.[4,5]

In order to evaluate the relative merits of

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This investigation has been aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

Liberal supplies of Elkosin and the Elkosin Triple Mixture were made available through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

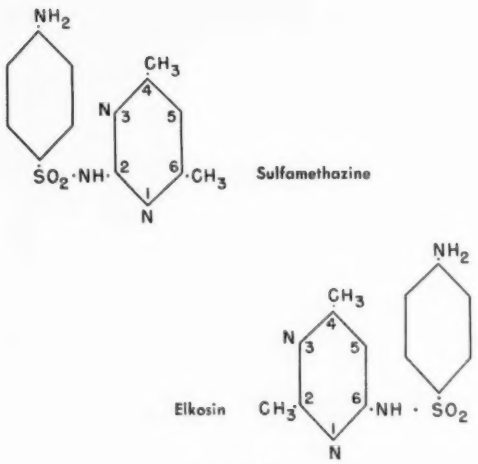

FIGURE 1.

elkosin under conditions comparable to those previously applied to other sulfonamide drugs,[6,7] a series of experimental studies were carried out at the Department of Pharmacology of New York Medical College. While the results of these investigations will be the subject of a separate report, it seems appropriate to outline briefly some of the pertinent findings. Incidentally, they confirmed to a large extent the findings of other authors.[2,3,8,9]

Elkosin was found to be substantially more soluble than any of the other sulfapyrimidines used. In fact the solubility of the "free" drug remains so high in the most acid physiologic *p*H range of human urine that the danger of massive crystalluria and mechanical renal obstruction appears eliminated in routine therapy. Elkosin is the only sulfapyrimidine which would not require adjuvant alkali therapy if used alone in full dosage. Unfortunately the N^4 acetyl derivative of this compound—a product of its metabolism in the body—is only sparingly soluble. This drawback is offset to a considerable extent by the low degree of in vivo acetylation of elkosin. In contrast to this observation the isomer sulfamethazine shows high percentages of acetylation in man and in experimental animals.

On the basis of equal dosage the toxicity of elkosin in laboratory animals was observed to be significantly lower than that of any of the other sulfadiazine derivatives used clinically. In addition this compound showed satisfactory properties with regard to absorption from the oral and parenteral routes of administration as well as with regard to its renal elimination. Finally, in human beings a mixture of sulfadiazine - sulfamerazine - elkosin (equal partial amounts) permitted the maintenance of satisfactory therapeutic blood and urine levels on a routine dosage schedule. In view of these findings it was felt that elkosin might be well suited as a component of a sulfapyrimidine mixture.

Therapeutic trials were carried out with an elkosin triple mixture (sulfadiazine-sulfamerazine-elkosin in equal partial amounts) in a series of 127 unselected adult patients suffering from acute infections. The results of this clinical study form the subject of the present report.

Procedure

As a rule, each patient initially received 4 gm. of the elkosin triple mixture by mouth, followed by 1 gm. every four hours day and night until defervescence and general clinical improvement occurred, when the dose was reduced to 1 gm. every six hours and continued for one or two more days. No alkalizing agents were used but the fluid intake was maintained at about 3000 cc. in 24 hours. The sediment from freshly voided specimens of urine was examined daily under the microscope for "sulfa" crystals, hematuria and casts. Blood was drawn from the antecubital vein almost daily at 9 A.M. for determination of free and total sulfonamide concentration. Complete blood counts were done at frequent intervals during the course of the disease.

Attempts were made to confirm initial clinical impressions with the help of laboratory examinations, such as roentgenologic studies and cultures of sputum, blood or urine, *prior* to institution of therapy. This was not always possible either because of the serious condition of some of the patients or because of technical difficulties when larger groups of patients were admitted simultaneously, especially at night.

Blood samples were assayed by the Bratton and Marshall method.[10] Obviously no differentiation could be made between sulfadiazine and its monomethylated and dimethylated derivatives with this procedure in determinations of triple mixture concentrations. All sulfonamide values were expressed as sulfamerazine equivalents since this compound represents the actual mean molecular weight of the three sulfapyrimidines. It should be stressed in this connection that inaccuracies of estimation due to individual differences of sulfadiazine, sulfamerazine and elkosin, with regard to absorption, conjugation and excretion, should be expected to result in errors of minor proportions only, because of the close chemical relationship of the three drugs and the consequent close similarity of their color reaction in the analytic method.

Results

Of the 127 cases treated with the elkosin mixture, the effectiveness of therapy could be evaluated unequivocally in 89 patients. The remaining 38 cases were not included in this statistical analysis because a clearcut interpretation of *therapeutic* results was not possible for one of the following reasons: (1) The patients were started simultaneously on combined sulfonamide and antibiotic therapy because of the extreme seriousness of their conditions. (2) They were started on antibiotics before being transferred to our wards where they were continued on the elkosin mixture. (3) Administration of the elkosin mixture had to be interrupted and the patient continued on other chemotherapeutics because our supply of the drug became exhausted and could not be immediately replenished. In all 38 cases the elkosin mixture was given for a sufficiently long period of time (minimum of three to five days) to permit their inclusion in the over-all evaluation of sulfonamide blood levels and toxic reactions encountered.

The results in 56 representative cases, illustrated in Table 1, demonstrate a very satisfactory range of blood levels and high therapeutic efficiency of the elkosin triple mixture as well as a low incidence of toxic reactions. Blood concentrations of free sulfonamide were readily maintained in most instances between 7 and 15 mg. per cent. The degree of acetylation in the blood was remarkably low, ranging between 2 and 15 per cent of the total concentration.

The series included 56 patients with various types of pneumonia of whom 45 patients or 80 per cent were cured by the elkosin mixture. Most of the remaining 11 pneumonias responded eventually to AUREOMYCIN® or CHLOROMYCETIN® therapy which suggests that they might belong in the group of so-called atypical or virus pneumonias. Another interesting finding was the high curative rate in genitourinary infections (9 cases out of 14). Although the group is small this result in usually obstinate infections appears remarkable.

Although no alkalizing agents were employed, crystalluria of a very mild degree was encountered in but 3 instances (cases 2 and 47 of Table 1 and 1 other not tabulated). No hematuria or any other signs of renal irritation attributable to the drug were observed in this series. There were 2 cases of dermatitis (19 and 25) apparently caused by the elkosin mixture and 2 cases of fever (5 and 9), possibly due to drug administration, making a total of 4 patients (3.7 per cent) with possible sensitization reactions.

Vomiting in moderate degree was seen in 2 patients. One patient with acute tonsillitis (15) responded well to sulfonamide administration, but vomiting occurred on the fourth day of therapy. The treating physician then administered penicillin by the intramuscular route, in addition to the elkosin mixture, in order to insure the maintenance of adequate chemotherapeutic blood levels. Although vomiting persisted after each dose of the elkosin mixture, it was not severe and actually permitted the maintenance of satisfactory sulfonamide concentrations in the blood. The second case (43) showed excellent response to therapy with defervescence within 24 hours, but vomiting developed after two days and increased in intensity so that it was decided to discontinue elkosin mixture therapy on the fourth day and to substitute penicillin. No other serious reactions were observed in any of the patients receiving the elkosin.

TABLE 1

RESULTS OF THERAPY WITH THE TRIPLE MIXTURE: SULFADIAZINE-SULFAMERAZINE-ELKOSIN

CASE	SEX	AGE	FINAL DIAGNOSIS	X-RAY REPORT	DAYS TREATED	SULFONAMIDE		THERAPEUTIC RESPONSE	TOXIC REACTIONS	REMARKS
						Total dose (gm.)	*Maintenance level in blood (mg. % free)*			
1	M	28	Lobar pneumonia	Consolidation R.L.L.	5	28	7-10	Cured	None	Responded well
2	F	65	Bronchopneumonia	Irregular clouding left base	6	38	12	Cured	None	Good result. Few crystals in urine
3	F	39	Pneumonitis	Clouding left base	7	43	8	Negative	None	Alpha streptococci and pneumococci in sputum culture. No response to sulfonamides but finally to chloramphenicol
4	M	46	Pyelonephritis		9	54	10-18	Cured	None	
5	F	40	Pulmonary emphysema	Pulmonary emphysema	4	26	10-15	Negative	None	Temperature of undetermined origin persisted at 99° to 101° F. No response to antibiotics
6	F	73	L.L.L. pneumonia	Clouding left base: cardiac enlargement	9	27	6-10	Cured	None	Patient also had heart failure—good results with digitalis
7	M	50	Bronchopneumonia	Thickening of both hilar regions; numerous densities in right lung	5	33	Not determined	Cured	None	
8	M	23	Pneumonia L.L.L.	L.L.L. pneumonia	8	51	8-11	Cured	None	
9	F	67	Bronchopneumonia	Bilateral pneumonia	7	39	7-12	Cured	Drug fever	Patient spiked temperature of 103° F. after afebrile for 3 days. Probably due to sensitization
10	F	76	Bronchitis	No pulmonary pathology	7	40	16-24	Cured	None	
11	F	32	Acute tonsillitis and pharyngitis		7	40	17	Cured	None	
12	F	30	Pneumonitis	Clouding L.L.L. field	5	28	12-14	Cured	None	Rapid improvement

TABLE 1 *(continued)*

RESULTS OF THERAPY WITH THE TRIPLE MIXTURE: SULFADIAZINE-SULFAMERAZINE-ELKOSIN

CASE	SEX	AGE	FINAL DIAGNOSIS	X-RAY REPORT	DAYS TREATED	SULFONAMIDE		THERAPEUTIC RESPONSE	TOXIC REACTIONS	REMARKS
						Total dose (gm.)	*Maintenance level in blood (mg. % free)*			
13	M	56	Lobar pneumonia	Pneumonia L.U.L.	8	48	6-7	Cured	None	
14	F	63	Pneumonitis	Pneumonitis right lung field	14	84	6-10	Negative	Drug fever ?	Rise in temperature on 6th day may have been caused by sulfonamides
15	F	35	Acute tonsillitis		8	46	10	Cured	Vomited	Because of vomiting on 4th day of therapy penicillin was given in addition to sulfonamides
16	F	24	Acute tonsillitis and pharyngitis		3	18	15	Cured	None	Patient transferred to Bellevue Psychotic Ward
17	M	45	Pneumonia	R.M.L. consolidation	7	41	Not determined	Cured	None	
18	F		Pneumonitis	Pneumonitis left base	5	28	10	Cured	None	
19	F	43	Pneumonitis	Pneumonitis R.M.L.	10	58	7-15	Cured	Rash	Dermatitis developed 3 days after drug was stopped. Responded to PYRIBENZAMINE®
20	F	48	Bilateral pneumonia	Bilateral pneumonia	10	58	10-11	Negative	None	Responded to chloramphenicol
21	M	45	Lobar pneumonia	Clouding R.L.L.	5	36	Not determined	Negative	None	Finally responded to chloromycetin
22	F	46	Pneumonitis	Pneumonitis R.U.H., L.L.L.	10	58	8-12	Cured	None	Also received penicillin
23	F	23	Pneumonitis	Pneumonitis L.L.L.	16	94	9-11	Negative	None	Responded to aureomycin
24	M	67	Bronchopneumonia	Clouding of ½ R.L.L. field	12	70	14-17	Cured	None	
25	M	43	Acute upper respiratory infection	Negative	7	39	Not determined	Cured	Rash	Response good but rash developed on face and hands, probably due to sulfonamides

TABLE 1 *(continued)*

RESULTS OF THERAPY WITH THE TRIPLE MIXTURE: SULFADIAZINE-SULFAMERAZINE-ELKOSIN

CASE	SEX	AGE	FINAL DIAGNOSIS	X-RAY REPORT	DAYS TREATED	SULFONAMIDE		THERAPEUTIC RESPONSE	TOXIC REACTIONS	REMARKS
						Total dose (gm.)	*Maintenance level in blood (mg. % free)*			
26	M	23	Pneumonia right base	Clouding right base	3	19	10	Cured	None	
27	M	79	Pneumonia R.L.L.	Irregular clouding R.L.L. field	13	80	11-12	Cured	None	
28	M	47	Pneumonia R.L.L.	Clouding right base	7	42	13	Cured	None	Prompt response
29	M	45	Lobar pneumonia	Homogeneous clouding L.L.L. field	6	37	12	Cured	None	
30	M	61	Pyelonephritis		20	76	8-11	Cured	None	Patient originally had carcinoma of prostate and metastases
31	M	40	Lobar pneumonia	Irregular clouding R.L.L.	5	34	Not determined	Cured	None	
32	M	49	Septicemia	Lungs clear	8	21	7	Negative	None	Beta hemolytic streptococci found in blood. Controlled by multiple antibiotics
33	M	48	Pneumonitis	Clouding right base	9	54	12-18	Cured	None	
34	M	21	Acute pyelonephritis		7	44	10	Negative	High temperature	Severe pyelonephritis due to enterococcus finally controlled by large doses of penicillin and streptomycin
35	M	34	Acute tracheobronchitis	Lungs clear	7	43	8-11	Cured	None	
36	M	36	Pneumonia R.L.L.	Clouding right base	5	34	10-15	Cured	None	
37	F	15	Pneumonia	Consolidation left base	11	70	8-10	Cured	None	
38	M	61	Bronchopneumonia	Bilateral clouding	7	37	16	Cured	None	
39	M	70	Pneumonitis	Increased density left base	13	82	11	Cured	None	
40	M	96	L.L.L. pneumonia superimposed on bronchiectasis	Clouding of L.L.L. field	14	72	10-15	Cured	None	
41	M	70	Acute pyelonephritis		21	126	8	Improved	None	Marked improvement
42	F	27	Pneumonia	Homogeneous clouding left base	10	60	6-11	Negative	None	No response to antibiotics

TABLE 1 *(continued)*

RESULTS OF THERAPY WITH THE TRIPLE MIXTURE: SULFADIAZINE-SULFAMERAZINE-ELKOSIN

CASE	SEX	AGE	FINAL DIAGNOSIS	X-RAY REPORT	DAYS TREATED	SULFONAMIDE		THERAPEUTIC RESPONSE	TOXIC REACTIONS	REMARKS
						Total dose (gm.)	*Maintenance level in blood (mg. % free)*			
43	M	34	Pneumonitis R.M.L. field	Hazy clouding	3	16	Not determined	Cured	Vomited	Excellent initial response but vomiting. Recurrence after elkosin mixture was reintroduced
44	F	45	Pneumonia	Diffuse infiltration R.U.L.	5	30	8-11	Negative	None	No response in 5 days. X-ray and history suggest TB but tests negative
45	M	83	Bronchiectasis and pneumonitis	Pulmonary fibrosis, probable bronchiectasis clouding lower third, right middle lung field	6	36	9-13	Cured	None	
46	M	71	Bronchiectasis and pneumonitis	Patchy clouding lower half of lung field	14	82	5-7	Cured	None	Alpha streptococci and *Staphylococcus albus* found in sputum
47	F	15	Pyelitis	Lungs clear	10	60	11	Cured	None	Few crystals in urine
48	F	78	Pneumonitis R.M.L.	Clouding mid portion right base	4	24	16	Cured	None	Rapid response
49	M	49	Pneumonia	Dense clouding upper ⅔ L.L. field	4	20	9	Negative	None	Responded to prolonged course of penicillin and streptomycin
50	M	73	Unresolved pneumonia	Dense clouding R.L.L.	12	72	5	Improved	None	Cured in combination with antibiotics
51	F	25	Lobar pneumonia	Pneumonitis right middle and lower lung field	4	22	Not determined	Cured	None	Rapid response
52	F	23	Pyelonephritis due to *Escherichia coli*		10	60	7-9	Cured	None	Very good result
53	M	44	Pyelitis *(Aerobacter)*		23	140	14	Cured	None	
54	F	55	Abscess left breast (postoperative infection)		10	64	9-15	Cured	None	Patient had rise in temperature after operation
55	M	29	Acute tonsillitis	Lungs clear	2	14	5-10	Cured	None	
56	F	44	Pyelitis		4	22	7-12	Improved	None	Marked clinical improvement

Summary

Therapeutic trials were carried out with a new sulfapyrimidine triple mixture in which the sulfamethazine component was replaced by its isomer, elkosin. This mixture of sulfadiazine-sulfamerazine-elkosin (equal partial amounts) was administered on a routine dosage schedule to a total of 127 adult patients suffering from acute infections.

Therapeutic results in sulfonamide-sensitive infections were highly satisfactory and the incidence of toxic reactions was remarkably low. Crystalluria was rare despite the omission of alkalization and no signs of renal irritation were observed. There were 2 instances of nausea and vomiting and 4 reactions possibly allergic in nature. No other untoward signs or symptoms were encountered.

On the basis of these results it was concluded that the sulfapyrimidine triple mixture sulfadiazine-sulfamerazine-elkosin, compared favorably with other triple mixtures of sulfonamide drugs used at present.[1, 11-14]

The technical assistance of Murray Pozner is gratefully acknowledged.

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Postgraduate Clinical NOTES

5. EFFECTS OF CALORIE DEFICIENCY

One deep impression made by the experience during the war is that deficiency of energy intake is associated with signs of a very characteristic nature, signs more immediately recognizable than any of those associated with lack of vitamins or protein about which so much has been written. From the practical standpoint the consequences of energy deficiency are vastly more important than those of any other shortage. They affect morale surprisingly quickly. Discontent, grumbling, and irritability are characteristic signs associated with a reduction in calorie intake of the order of 20 per cent, particularly when it affects those engaged in physical work. The loss of weight related closely to the negative calorie balance is of less importance than the disturbances of mental balance.

Sir Jack Drummond, Nutritional Problems and Civilian Defense,
Public Health Reports, September 1952, p. 859

Retinal Arteriolar Signs of Hypertension

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There are four grades of the three main types of ophthalmoscopic hypertensive signs which occur in the retinal arterioles. Acute and chronic hypertension can be differentiated on the basis of these signs and, therefore, a better evaluation of the treatment can be achieved. The changes occurring in the retinal arterioles are illustrated by both diagrams and photographs.

It is known that the arterioles of patients who have vascular hypertension are essentially normal early in the clinical course of the disease. As the process increases, however, changes in the arterioles occur which tend to become progressively more advanced in proportion to the severity and the duration of the hypertensive process. As a result of this, advanced changes usually occur in the systemic arterioles during the end stages of the disease.

Since there is a tendency for the retinal and systemic arterioles to be similarly involved in this process, an estimation of the type and degree of the ophthalmoscopic signs of retinal arteriolar hypertension is frequently very helpful in the clinical evaluation of the patient's condition.

It is well known that the clinical course of hypertension may be relatively rapid (acute hypertension) in some patients and relatively insidious (chronic hypertension) in others. It is not so well known that the retinal arteriolar signs, when properly interpreted, may indicate which of these courses the disease is most likely to pursue, because the signs are quite different and characteristic for the rapid and slow forms of the disease. It is therefore impossible to overestimate the importance of making the distinction between the relatively rapid and the chronic form of the disease on the basis of the retinal arteriolar signs, especially since attempts to evaluate medical or surgical results are much less meaningful when the chronic and the acute form of hypertension are not differentiated.

The interpretation of the retinal signs of hypertension is neither easy nor simple. It is understandable that authorities are not in agreement on many aspects of this problem when one considers the variations in the clinical course, the coexistence of more than one form of hypertension with other forms of diffuse vascular disease, and the difficulties in correlating ophthalmoscopic and microscopic findings.

The purpose of this article is to describe the ophthalmoscopic characteristics and the usual clinical significance of the four grades of the three main types of retinal arteriolar signs of hypertension. Such signs as sheathing, occlusions and tortuosity are excluded because they occur infrequently and have less prognostic significance.

These retinal arteriolar signs are illustrated by the schematic drawings and fundus photo-

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graphs which were exhibited at the 1951 convention of the American Medical Association. The grading and grouping of these signs are based essentially on the report of the Committee on the Classification of Hypertensive Disease of the Retina of the American Ophthalmological Society.[1] The literature on this subject is so extensive that no attempt is being made to give proper credit where it is due.

There are three main types of retinal arteriolar signs which occur in hypertension. They are (1) generalized narrowing, (2) focal constrictions and (3) generalized arteriolar sclerosis. The first two are associated with those types of hypertension which pursue a relatively rapid clinical course. The third, generalized arteriolar sclerosis, is characteristically associated with the form of hypertension whose clinical course is one of insidious progression. Each of these three types may be separated into four grades, each grade representing an increasing degree of arteriolar involvement. Mixed combinations of these signs are frequently encountered. The grading is not intended to be an exact science, and slight variations in interpretation may occur.

Generalized Narrowing

Generalized narrowing is a term used to describe a uniform caliber reduction of the retinal arterioles. The term is used to differentiate this type of narrowing from the nonuniform focal constrictions. The essential difference is that generalized narrowing involves a great extent of the vessel whereas focal constrictions involve only a very short extent of the arteriole. Generalized narrowing may involve either the peripheral third or the entire length of a single arteriole; the entire arteriolar tree is not necessarily narrowed. The transition from the non-narrowed to the narrowed portion is so gradual that the exact point of the beginning of the narrowing is frequently difficult to locate. While the exact mechanism of this sign has not been established, the consensus is that it is due to increased tonus in the arteriolar musculature.

Ophthalmoscopically, the arteriole appears narrowed, and there is slight, if any, accentuation of the reflex stripe and no decreased visibility of the arteriolar wall. It is recognized by comparing the ophthalmoscopist's concept of the normal width of the arteriole with the width of the hypertensive patient's arteriole, and also by recognizing that the normal arteriovenous ratio of 2:3 has been decreased by the arteriolar narrowing (Figure 1). In view of the many individual optic and anatomic variations, it would seem that the incidence of interpretative errors might be sufficiently high to invalidate the sign, but this seldom occurs with trained observers.

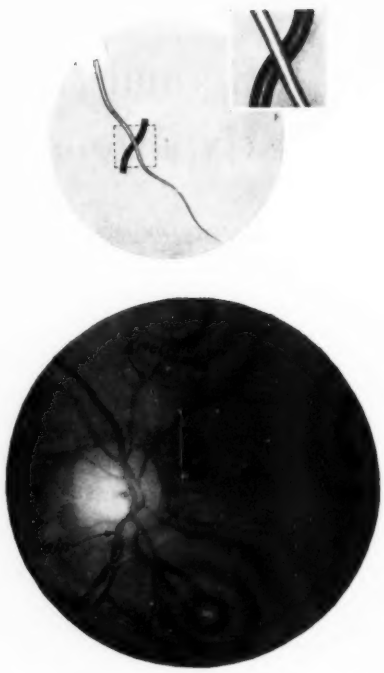

FIGURE 1. The normal fundus oculi. The normal arteriolar-venous ratio is 2:3. This is shown in the upper schematic diagram, and by the lower photograph. In the diagram the vessels are shown as foreshortened to include the entire length of the arteriole in a single picture.

The differential diagnosis involves the proper evaluation of apparent narrowing due to high hyperopia, to relatively large veins, to several arterioles supplying the same retinal quadrant and to postinflammatory narrowing. It is differentiated from the senile arteriolar

narrowing by the loss of luster in the latter.

The concept that generalized narrowing is the primary cause and the pathologic mechanism which produces the increased peripheral resistance, thus creating the increased blood pressure, seems less likely than the view that generalized narrowing represents a restitutional vascular reaction which decreases the blood flow through the retinal capillaries in the presence of hypertension. If the inference that this sign is due to increased contraction of arteriolar muscles is correct, it is understandable why it cannot be demonstrated histologically. Generalized narrowing almost invariably precedes focal constrictions, and is therefore frequently encountered without other signs of the disease.

Generalized Narrowing, Grade I

When the arteriole is reduced to approximately three-fourths the width of a normal arteriole, grade I generalized narrowing is said to be present (Figure 2). This slight reduction in caliber may be routinely overlooked unless a careful search is made for it. With experience it becomes possible to estimate this amount of caliber reduction visually as accurately as it might have been measured by a retinal graticule.

Grade I generalized narrowing is usually found limited to the peripheral third of the nasal arterioles, but may occasionally involve most of the arterioles and be found in the periphery of the temporal arterioles.

Generalized narrowing is frequently the first sign of hypertension. It is usually found in patients whose hypertension is, as yet, of short duration and minimal degree. The characteristic diastolic blood pressure range is from 90 to 95 mm. of mercury. The clinical course of the hypertension may regress, as is the case in the hypertensive toxemias of pregnancy, when the arterioles frequently return to their normal caliber. On the other hand, the hypertension may continue to progress, in which case higher grades of generalized narrowing may subsequently develop.

This initial sign of hypertension is almost never associated with hypertensive symptoms or retinopathy. If retinopathy is present, even if the blood pressure is higher than the usual range for this finding, a nonhypertensive cause for the retinopathy should be suspected. Even if cardiac, renal or cerebral signs or symptoms are present, it is unlikely that they are due to the hypertension.

FIGURE 2. Generalized retinal arteriolar narrowing, grade I.

The interpretation of this finding is that the hypertension has not, as yet, been of sufficient severity or duration to produce structural changes in the retinal arteriolar tree, nor, by inference, in the systemic arterioles. If the cause can be removed, it is most probable that the patient's vascular tree will return to normal and the hypertensive process will not undergo further progression.

The prognosis is relatively good.

Patients with grade I generalized narrowing warrant very careful medical management because they are more favorable for treatment, since the vascular process may be reversible.

Patients at this stage do not warrant surgi-

FIGURE 3. Generalized arteriolar narrowing, grade II.

cal intervention of the sympathetic nervous system.

Generalized Narrowing, Grade II

In generalized narrowing, grade II, the narrowed portion of the arteriole is reduced to one-half of the width of a normal arteriole (Figure 3). This degree of narrowing, while easily overlooked, is more obvious than grade I. By comparing the schematic diagrams it can be seen that the arteriolar reflex stripe is not seen as far toward the periphery as it is in grade I, and the arteriovenous ratio is more obviously reduced. Grade II generalized narrowing usually involves at least the peripheral half of the nasal arterioles and may be seen frequently in the temporal arterioles. It may occasionally involve the entire retinal arteriolar system. This degree of involvement is usually not associated with symptoms, and retinopathy is found infrequently.

Grade II generalized narrowing is usually associated with hypertension of moderate severity and short duration. The characteristic diastolic blood pressure range is approximately 95 to 100 mm. of mercury.

The hypertensive course is frequently progressive and the probabilities of complete regression are less than in grade I.

The interpretation of this finding is that the hypertension has not, as yet, been of sufficient severity or duration to produce arteriolar structural changes. It may be reversible.

The prognosis is fairly good.

The indications for medical treatment are more urgent than in grade I. Surgical treatment is usually not warranted at this time.

Generalized Narrowing, Grade III

In generalized narrowing, grade III, the narrowed portion of the arteriole is reduced to one-fourth of the width of a normal arteriole. This degree of narrowing is more difficult to overlook. When generalized narrowing, grade III, is present, almost all the retinal arteriolar tree is usually involved, as illustrated in Figure 4.

Focal constrictions are frequently associated with this degree of generalized narrowing. Symptoms and signs of hypertension and retinopathy are frequently encountered with grade III generalized narrowing.

It is usually associated with hypertension of short duration but of marked severity. The characteristic diastolic blood pressure range is from 105 to 120 mm. of mercury.

The hypertensive course is usually progressive and sclerosis usually occurs if the patient lives sufficiently long.

The interpretation of this finding is that the hypertension is very severe and the clinical course is most likely to be one of rapid progression.

The prognosis is unfavorable.

If the general signs and symptoms warrant it, sympathectomy is indicated.

Generalized Narrowing, Grade IV

In generalized narrowing, grade IV, the arteriole is reduced to linear proportions. The term "spasm" is sometimes used to indicate maximum involvement. This degree of narrowing may involve only portions of one or

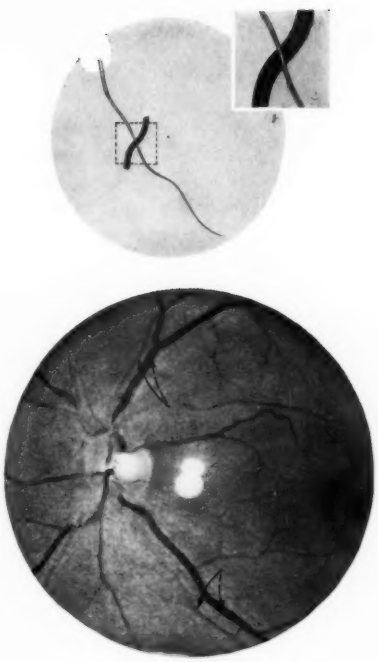

FIGURE 4. Generalized arteriolar narrowing, grade III.

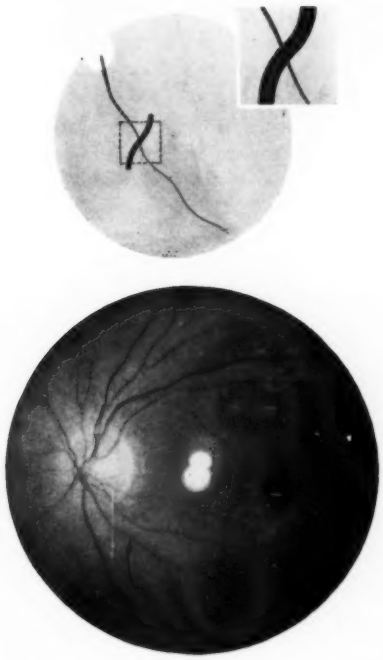

FIGURE 5. Generalized arteriolar narrowing, grade IV.

may involve all the arterioles. It is usually distributed irregularly in the arteriolar tree. It is not a frequent finding since a fatal issue may precede this degree of involvement. It is illustrated in Figure 5. Symptoms, signs and retinopathy are usually marked. The characteristic diastolic blood pressure is above 120 mm. of mercury.

Regression almost never occurs and sclerosis is inevitable if the patient lives long enough.

The prognosis is extremely unfavorable. Surgery of the sympathetic system may occasionally produce a dramatic improvement.

Focal Constriction

The second type of arteriolar sign in hypertension is called *focal constriction*. The term focal is used because each one of these lesions involves only a very short extent of the arteriole. Unlike generalized narrowing, the beginning and the end of the involved area are easily recognized because the arteriolar wall is acutely constricted on each side at the point of involvement, as illustrated in Figures 6 through 9. Initially these lesions are located in the peripheral or middle third of the arteriole and as the disease progresses the focal constrictions become more numerous, occur closer to the disk, and the amount of the constriction increases.

Focal constrictions occur in a functional and a sclerotic form. The former may be transitory while the latter is permanent. In the functional or spastic form the visibility of the arteriolar wall is not increased in the area of the constriction, whereas in the sclerotic form the arteriolar wall may become visible at the constricted point. The differentiation of these two types of focal constriction is frequently impossible.

The only lesions which require differential diagnosis from hypertensive focal constrictions are the irregular caliber reductions of postinflammatory or postedematous secondary adventitial fibrosis. These secondary changes do not have the generalized and even dis-

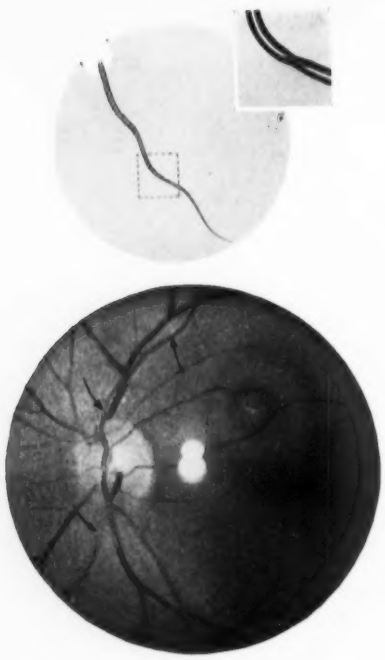

FIGURE 6. Focal arteriolar constriction, grade I.

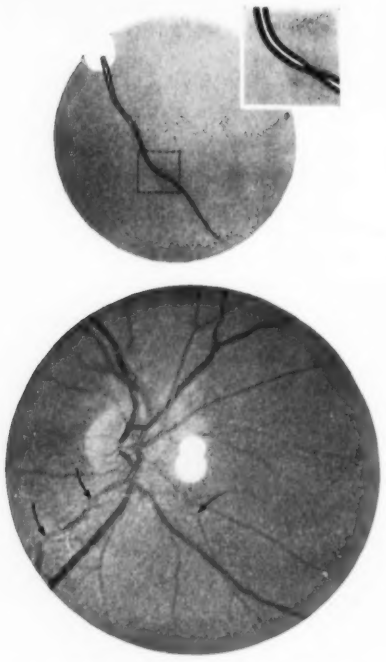

FIGURE 7. Focal arteriolar constriction, grade II.

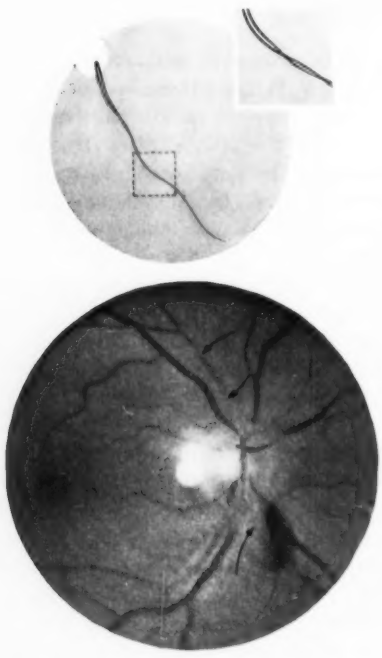

FIGURE 8. Focal arteriolar constriction, grade III.

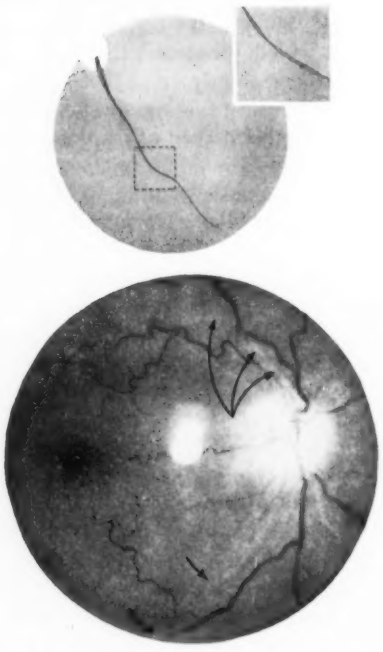

FIGURE 9. Focal arteriolar constriction, grade IV.

tribution of the hypertensive signs. They are more irregular and are usually associated with and related to other signs of previous inflammation adjacent to the involved area. They are not more marked in the periphery, as are the hypertensive signs.

The cause of these focal constrictions is controversial, but one of the more likely possibilities is that they represent at first contractions and later contractures of the precapillary smooth muscle sphincters in the arteriolar wall. This inference is based on the experimental work of Shorr[2] and his colleagues, and on the clinical evidence that they disappear, entirely or in part, following the termination of pregnancy in the hypertensive toxemia, and also following sympathectomies in hypertension. If they are muscular contractures, it would also explain the failure of many individuals to progress from grade I to grade II, then grade III and on to grade IV. This concept is in need of confirmation.

Focal Constriction, Grade I

In grade I focal constriction the caliber of arteriole in the constricted portion is reduced to approximately two-thirds of the caliber of the normal portion of the arteriole, just central to the area of the constriction. This means a narrowing of one-third in the proximal portion of the arteriole. It is easily overlooked. Allowance must be made when these relationships are modified by the presence of generalized narrowing, which is not infrequently present in the same vessel at the same time as focal constriction (Figure 6).

Usually only two or three constrictions are found in any one arteriole in grade I. It is necessary to search all the way to the periphery for these signs.

Systemic signs and symptoms and retinopathy are not usually encountered when the retinal arterioles reveal only grade I focal constriction. An exception may occur when the more marked degrees of generalized narrowing are superimposed on the grade I focal constrictions.

The functional variety of grade I focal constriction is usually associated with hypertension of relatively short duration and moderate severity. The sclerotic focal constrictions are usually associated with moderate duration and moderate severity of the hypertension. The usual diastolic blood pressure range is from 95 to 110 mm. of mercury.

The prognosis is fairly good. Patients with this minimal involvement do not usually warrant sympathectomy.

Focal Constriction, Grade II

In grade II focal constriction the arteriolar caliber is reduced to one-half of normal. The number of constricted areas are increased so that from about three to six areas may be found in any one arteriole. This degree of involvement is illustrated in Figure 7.

Unlike grade I focal constriction, cerebral, cardiac and renal, as well as retinal, signs and symptoms are frequently encountered. Grade II focal constriction may be associated with hypertension of moderate severity and moderate to prolonged duration. Some patients are observed in whom the grade of focal narrowing increases from grade I to II, III and on to grade IV. Quite frequently, however, patients are seen in whom this progression does not take place and they may remain for many years without increased focal constriction. A possible interpretation of the significance of the absence of the progression is that in this case the focal narrowing is not an inherent progressive phenomenon but rather a restitutional reaction to the elevation of pressure by which blood flow in the capillaries is kept at normal levels. The usual diastolic blood pressure range is from 110 to 120 mm. of mercury.

The clinical course of hypertension in which grade II focal constriction is encountered may be variable. Following an indefinite period, an acute excerbation of the disease may be associated with a sudden blood pressure rise above the previous level, the development of retinopathy and severe systemic signs and symptoms, and a fatal termination, without further progression to the more advanced grades of focal constriction. The prognosis is, however, usually good with grade II focal constriction. The response of the patients with grade II focal constriction

FIGURE 10. Generalized arteriolar sclerosis, grade I.

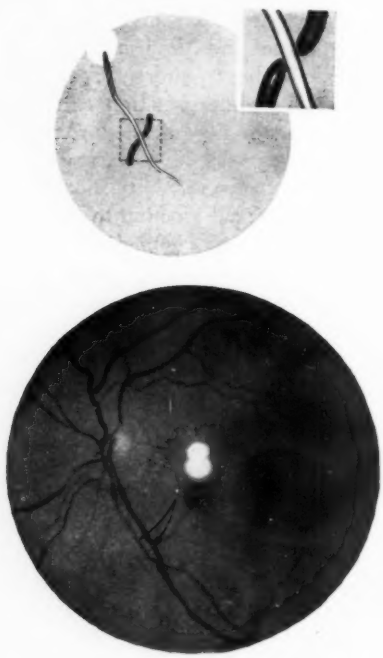

FIGURE 11. Generalized arteriolar sclerosis, grade II.

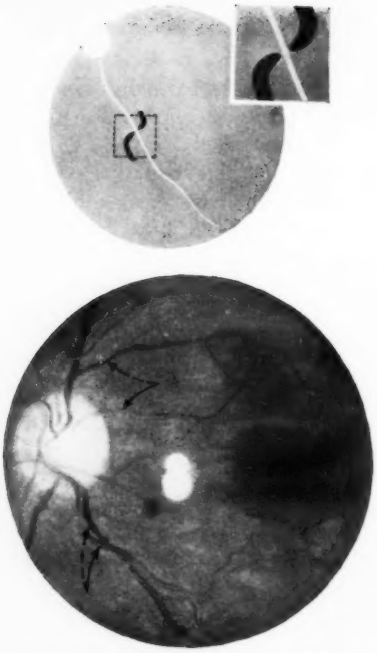

FIGURE 12. Generalized arteriolar sclerosis, grade III.

to surgical therapy may vary from a disappointing result to a dramatic improvement.

Focal Constriction, Grade III

In grade III focal constriction the caliber of arteriole in the constricted area is reduced to one-third of the caliber of the proximal portion of the arteriole (Figure 8).

There is usually an associated marked generalized narrowing of most of the retinal arteriolar tree when this degree of focal constriction is present. The number and the distribution of focal constrictions are increased so that 6 to 10 constrictions may occur in one arteriole. Retinopathy and systemic signs and symptoms are frequently associated with this degree of arteriolar involvement. The diastolic blood pressure usually ranges from 120 to 140 mm. of mercury.

The prognosis is much more grave than in grade II because relatively inactive periods in the progress of the disease are extremely unlikely to occur. If most of the focal narrowings are of the spastic variety, as occurs in hypertension of marked severity and short

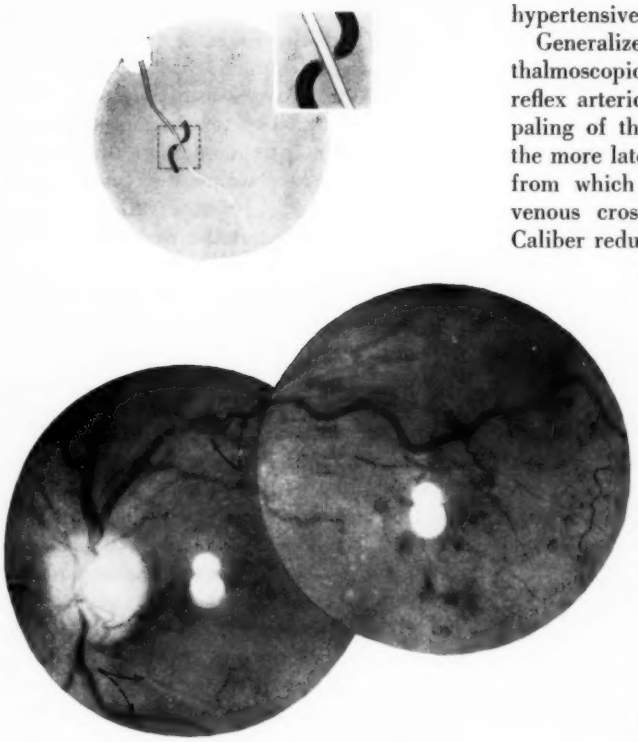

FIGURE 13. Generalized arteriolar sclerosis, grade IV.

duration, the relief of symptoms following sympathetic surgery may be most gratifying.

Focal Constriction, Grade IV

In grade IV focal constriction the arteriole is reduced to linear proportions. Since most patients do not live to reach this degree of constriction, it is very rarely encountered. The prognosis is very poor and treatment is not associated with much success. This degree of involvement is illustrated in Figure 9.

Generalized Sclerosis

Generalized sclerosis is a term used to designate the retinal arteriolar signs which are associated with the type of hypertension that runs an extremely chronic course. Patients whose retinal arterioles have this type of change may frequently live from 15 to 20 or more years without developing serious hypertensive signs or symptoms.

Generalized sclerosis is characterized ophthalmoscopically by an accentuation of the reflex arteriolar stripe. There is also a slight paling of the blood stream which occurs in the more lateral portion of the arteriolar wall from which no reflex is obtained. Arteriovenous crossing signs are usually present. Caliber reductions are minimal or absent unless the patient is suffering concurrently from both the rapidly progressive and the chronic form of the disease, a combination of clinical findings that is frequently encountered. Whereas focal constrictions are practically pathognomonic of hypertension and are readily diagnosed, the diagnosis of generalized sclerosis requires more careful consideration. It has not been authoritatively established that this form of diffuse vascular disease is entirely independent of atherosclerosis. Most cases of advanced atherosclerosis are associated with arterioles of normal appearance. It is difficult to evaluate in the early stages, but when the complete fundal changes of this condition are present, including the venous changes, it is readily recognized.

Generalized sclerosis may be described as occurring in four grades.

Generalized Sclerosis, Grade I

Generalized sclerosis, grade I, is characterized by slight accentuation of the arteriolar reflex stripe and paling of the blood stream. There may be a slight obscuration of the vein where it lies posterior to the arteriolar wall at the point of arteriovenous crossing. The arteriolar caliber remains uniform and is not narrowed. This is illustrated in Figure 10. The most characteristic microscopic findings in this type of sclerosis is hyalinization of the media of the arteriole.

Generalized sclerosis, grade I, is not usually associated with significant systemic hypertensive signs or symptoms. The usual diastolic

blood pressure range is from 90 to 100 mm. of mercury. The signs are not reversible.

The prognosis is excellent even if the blood pressure is above the usual level and, therefore, treatment is not urgent when this minimal degree of involvement is present. Occasionally these signs occur in nonhypertensive individuals, and they are not as pathognomonic as are those previously described signs.

Generalized Sclerosis, Grade II

Generalized sclerosis, grade II, is characterized by a "copper wire" appearance of the reflex stripe and slight arteriovenous compressions (Figure 11). Generalized sclerosis, grade II, indicates a hypertension of several years' duration; nevertheless, the prognosis is still relatively favorable. There is no typical diastolic blood pressure range. Signs and symptoms are usually absent or minimal.

Generalized Sclerosis, Grade III

Generalized sclerosis, grade III, is characterized by a "silver wire" appearance of the reflex stripe and marked compression and beginning angulation of the vein at the point of arteriovenous crossing (Figure 12).

It is frequently, but not necessarily, associated with systemic signs and symptoms of hypertension. The prognosis is more guarded, as terminal malignant hypertension may occasionally be superimposed on the otherwise chronic clinical course.

Retinopathy is usually due to local venous occlusions and, therefore, does not have the serious prognostic significance of the retinopathy associated with focal constrictions.

Generalized Sclerosis, Grade IV

Generalized sclerosis, grade IV, consists of complete fibrosis of the arterioles (Figure 13). This degree of sclerosis is rarely encountered clinically. It represents the maximum degree of involvement. The prognosis is very poor, as major vascular accidents may occur at any time.

Difficulties in Classification

There are three main sources of difficulty in the evaluation of hypertension. These are lack of definitive terminology, the frequent coexistence of two or more forms of diffuse vascular disease, and the fact that the early and important changes are not readily available for microscopic examination. The classification and interpretation must therefore be based on inference rather than on incontrovertible evidence. The observation of these details is difficult and the deductions which have to be made are not easy, even for those who have had extensive experience in this field. Tortuosity of the main arterioles is not constantly associated with any type of hypertension and is a relatively infrequent and unimportant sign.

It is extremely difficult to obtain satisfactory photographic representation of all the various grades of the various signs of hypertension. While this method of illustrating the material is extremely valuable, it has many shortcomings. For this reason a diagrammatic illustration accompanies each photograph. This method likewise is not ideal. It is to be understood that the only way to obtain an adequate concept of the appearance of these lesions is to observe a large series of them with the ophthalmoscope through a well dilated pupil.

Summary

The three main types of retinal arteriolar signs are (1) generalized narrowing, (2) functional or sclerotic focal constriction and (3) generalized sclerosis. These signs have extremely important clinical implications in diagnosis and treatment. An understanding of these changes is helpful in the differential diagnosis of retinopathy and in the diagnosis of the cause of systemic signs and symptoms. An appreciation of the different types of arteriolar change is necessary to interpret the known facts of hypertension, and should be of value in unraveling the much more important unknown aspects of this complex subject.

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Pediatrics IN GENERAL PRACTICE

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Peptic Ulcer in Childhood

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THE practicing physician sees many children who complain of recurrent abdominal pain. Although it has not usually been considered in the differential diagnosis, recent studies indicate that duodenal ulcer is a common cause of recurrent abdominal pain in the pediatric patient.

Alexander[1] reported the first large series of children with duodenal ulcer. Morgan[2] stressed the need for thorough roentgenologic examination of the stomach and duodenum in evaluation of abdominal pain in children. Proctor[3] in 1925 showed that adults with proved ulcers often dated their symptoms back to childhood. Girdany[4] reported on the incidence of peptic ulcer among children seen at the Children's Hospital of Pittsburgh.

The pain associated with peptic ulcer in children is similar to that in adults. Most children wake at night because of pain, and complain of discomfort in the morning on arising. Pain in the evening before going to bed, and before meals, is quite common.

Some children volunteer that the ingestion of food, milk or alkalis brings them relief of their symptoms. A few children complain of recurrent episodes of vomiting, which often start during the night and awaken them.

Pain is usually referred to the umbilicus. During fluoroscopic examination most children point directly to the duodenal bulb as the localizing site of pain; deep palpation by the examiner over this area demonstrates marked tenderness. Although the characteristic pain story is often not volunteered, it can usually be elicited by direct questioning.

The incidence of peptic ulcer is the same in boys and girls. Children from the age of 3 years through adolescence may be affected. The duration of their symptoms varies from weeks to many years.

The roentgenologic signs of duodenal ulcer in children are the same as those in adults. These include pylorospasm, deformity of the bulb, folds radiating toward a crater, and a crater niche with a radiolucent zone surrounding it. Irritability of the bulb should not be

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used as a roentgenographic criterion of ulcer in children, since it is a usual finding in pediatric patients. Ulcer craters demonstrated in children are usually smaller than those seen in adults, and deformities of the bulb are less marked.

An 8 year old girl had a history of vomiting of three months' duration and weight loss of 30 pounds. A postbulbar ulcer was demonstrated on roentgenologic examination (Figure 1). This child improved temporarily on a dietary regimen in the hospital, but began vomiting again when she returned home. Surgical exploration was done and a gastroenterostomy performed. There was a postbulbar ulcer in the duodenum at the site demonstrated on the roentgenograms.

A 5 year old boy complained of recurrent abdominal pain on arising in the morning and of night pain interrupting his sleep. He had had symptoms for three years. In Figure 2 the roentgenologic findings of duodenal ulcer are seen. The child showed prompt improvement on ulcer therapy, and has remained symptom-free.

A 5 year old Negro girl complained of recurrent paraumbilical abdominal pain, preceding and aggravated by meals. The diagnosis of duodenal ulcer was confirmed by roentgenographic examination (Figure 3). She recovered completely on medical therapy. Four months later she had surgical repair of an umbilical hernia. Direct inspection of the duodenum at surgery showed multiple adhesions about the bulb characteristically associated with peptic ulcer.

Psychiatric studies have not been reported on large groups of children with peptic ulcer.

FIGURE 1. Spot film made following barium meal in an 8 year old girl with a history of vomiting of three months' duration and weight loss of 30 pounds. The arrow is directed to the site of the postbulbar ulcer. This diagnosis was later confirmed at surgery.

FIGURE 2. Ulcer crater, deformity in the bulb, and radiolucent zone surrounding the crater in a 5 year old boy with a history of recurrent abdominal pain for three years. There was prompt improvement on ulcer therapy and the patient has remained symptom-free.

Available observations indicate that children in this group are in many ways similar to their adult counterparts. They are usually bright and tense, and characterized by their parents as "nervous." They often seem lacking in overt emotional lability, and tend to keep things to themselves.

Treatment

Clinical recovery occurs rapidly after the institution of treatment. Bland diets and the elimination of fried, spicy and fatty foods are effective. Milk in the evening before retiring and between meals is useful. When a dietary regimen alone produces relief of symptoms, medicinal therapy is not necessary. Should medication be needed, any of the standard aluminum hydroxide mixtures in doses of ½ to 1 tablespoon four times a day may be given. BANTHINE® with or without dietary modification has proved effective in doses of 25 mg. two or three times daily.

Symptoms recur during periods of stress and during some febrile illnesses. Occasionally, for instance, children who have been asymptomatic on therapy vomit blood during the course of measles. Therefore, intensive dietary and medicinal therapy during febrile illnesses and periods of stress seems indicated.

Conclusions and Summary

1. Peptic ulcer occurs in childhood, and is a cause of recurrent abdominal pain.
2. There is no sex predilection.
3. The diagnosis of peptic ulcer in children should be suspected when there is a history of recurrent abdominal pain in a tense, bright youngster. There is usually a history of pain waking the child at night, and intense pain in the morning on arising.
4. Characteristic roentgenologic signs of duodenal ulcer can be demonstrated when multiple spot and pressure films of the bulb are made after barium meal.
5. Clinical improvement occurs rapidly after medical treatment is begun.

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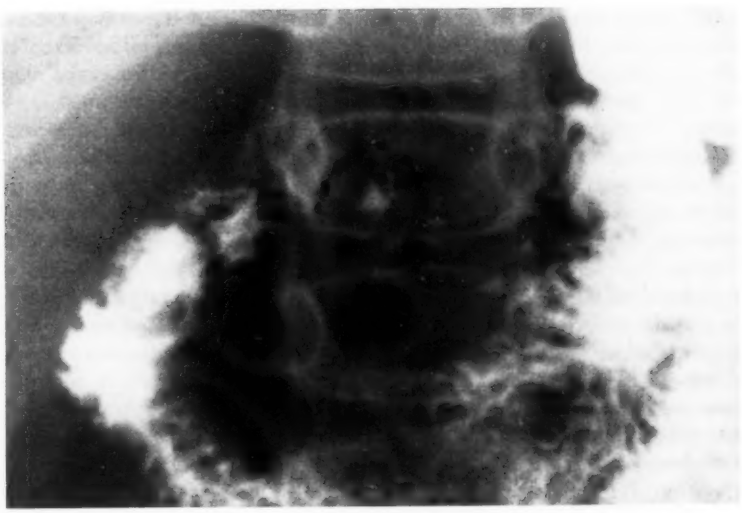

FIGURE 3. Folds radiating toward a small ulcer crater in the duodenum in a 5 year old girl with a long history of paraumbilical pain preceding and aggravated by meals. She improved promptly on medical treatment. The findings characteristically associated with duodenal ulcer were later identified at surgery for repair of an umbilical hernia.

Atopic Dermatitis in the Infant (Infantile Eczema)

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THE name "atopic dermatitis" (Sulzberger) has been generally accepted in this country as the designation for the condition formerly called "neurodermatitis disseminata." As the name implies, the dermatitis is thought to be intimately connected with a hereditary tendency to certain forms of allergy, the mechanism of which is identical with that of the classic examples of allergy, for example, hay fever and asthma—i.e., that type of inherited tendency to allergy which was named "atopy" by Coca.

It is still open to discussion whether or not it is permissible to accept a causal allergic mechanism in the large percentage of cases in which it cannot be established beyond doubt. From practical experience and clinical considerations I am inclined to believe that an allergy plays at least some part in most, if not all, cases of this dermatitis. Metabolic deficiency or focal infection has been rather vaguely suspected. Disturbances of the sweating mechanism have recently been pointed out by Sulzberger, Herrmann and Zak,[1] but their significance cannot yet be evaluated.

It is my conviction that neither the old hypothesis of the neurogenic origin of atopic dermatitis, which led Brocq to call it neurodermatitis, nor its modern rival, which tries to trace it to a "neurovascular instability," is on a sound basis. Babies and young children with this dermatosis usually show no signs of disturbances of the nervous equilibrium. Also, in older children one can find quite a number of patients whose physical and psychosomatic status is excellent. Of course, many children of school age with atopic dermatitis are high-strung. This, however, can be traced to the persistence of severe itching, the loss of sleep, etc., over a period of years. It is evident that they become irritable, eat poorly and show other signs of functional nervous disturbances. Even tests with the most elaborate methods of modern neurologic and psychosomatic examination do not result in convincing proof that these deficiencies are essential causes and not sequelae of the dermatologic changes.

Classification

Sulzberger and his co-workers were successful in demonstrating that in infancy and in childhood, atopic dermatitis represents a definite morbid entity, identical with the old "infantile eczema" and so-called "constitutional" dry eczema, and with "disseminated neurodermatitis" or "disseminated lichen simplex" in children beyond infancy. This new concept has simplified the fundamental problems of this controversial skin ailment. It has taught us that one must re-evaluate and broaden the complex of the former neurodermatitis disseminata, which must be regarded as the nucleus of atopic dermatitis.

Although this entity has been widely recognized, many of the latest reports on this subject still convey the impression that infantile eczema must be subdivided into three different dermatoses: atopic dermatitis, seborrheic dermatitis and contact dermatitis. In my opinion this division is incorrect and confusing.

Many years ago, influenced by Unna's original conception of seborrheic dermatitis, I tried to carry out such a subdivision.[2] It has never led to satisfactory results; I was, there-

fore, compelled to give up my futile attempts after realizing the full implications of Sulzberger's synthesis of atopic dermatitis.

There are, of course, instances of genuine, primary eczematous dermatitis in infancy, e.g., intertriginous dermatitis of the groins and intergluteal areas, papular gluteal erythema, érythème syphiloïde postérosive, and a very few others, but these have never before been regarded as true representatives of the former "diathetic" infantile eczema. They have previously been classified with artificial dermatitis, dermatitis venenata, etc. So-called "intertrigos" in the folds of the neck, the axillas and the creases of the arms and legs are often if not always due to atopic dermatitis. For these and other reasons I cannot agree with the contention that this condition (or intertrigo in general) is due primarily to an infection with streptococci.

Never having been regarded as true typical "infantile eczema," such cases should not, of course, be included under infantile atopic dermatitis. Even more misleading, however, is the present trend of almost all students of the subject to reserve a prominent place for seborrheic dermatitis in infants.

One of the main reasons for this mistake has been that Unna, despite his great merit in having demonstrated the morphologic differences between the classic types of seborrheic dermatitis and the "eczemas," later broadened the concept of seborrheic dermatitis to what appears to me to be an untenable degree. This can be seen from many of his papers, particularly his last article in Jadassohn's handbook.[3] It is regrettable that this has led Moro[4] and Finkelstein[5] to formulate their conception of "dermatitis seborrhoides" in infancy, an idea which I believe to be utterly misleading. The contention that dermatitis seborrhoides is caused by a disturbance of the fat metabolism of the skin is purely hypothetic. Claims that the eruption in infants responds to dietary regimens contradict common experience with the classic types of seborrheic dermatitis as seen in adults. The simple fact that atopic dermatitis in babies may benefit from elimination of foods demonstrates the shaky foundation of such an argument.

As a matter of fact, atopic dermatitis as it is known today imitates the most frequent types of seborrheic dermatitis, particularly in infancy (most commonly on the scalp but on the glabrous skin as well). Instances of "neurodermatitis disseminata," labeled seborrheic dermatitis, are found among case histories and pictures published by Moro and others. The existence of a seborrheic reactivity of the skin in children (Unna's "status seborrhoicus"; Darier's "kerose") must also be questioned. In my opinion it does not occur in infancy. Only two dermatoses deserve brief consideration with particular regard to their relation to seborrheic dermatitis:

1. Cradle cap—This rather unscientific term should be applied solely to eruptions on the crown of the scalp in young infants. (Usually all the erythematosquamous eruptions on the scalp of infants, including those of atopic dermatitis, are called cradle cap, as can be seen from pictures in the monographs of Moro, Finkelstein and others.) Its most impressive sign is the abundant, greasy, tightly adherent, gray or dark brown, scaly crust extending evenly over the entire crown in infants from 2 weeks to 1 month of age. After removal of the crust the skin under it appears blood red, shiny, varnished and perhaps a trifle moist. In my opinion this condition is not atopic, nor has it any characteristics which might lead to its inclusion with seborrheic dermatitis.

2. Leiner's disease (desquamative erythroderma)—I am now extremely doubtful whether it is permissible to consider this serious systemic ailment as a manifestation of seborrheic dermatitis. The symptomatology of the cutaneous eruption resembles in many ways that of seborrheic dermatitis as seen in adults (discoid patches on trunk; scaly crusts on scalp and eyebrows) but the systemic disturbances and the response to dietary treatment are inconsistent with this classification.

Neither can I support the existence of a seborrheic component of atopic erythroderma in infants. There is not the slightest reason for such an assumption, unless the faint resemblance of severe widespread infantile atopic dermatitis to Leiner's erythroderma

causes the atopic eruption to be mistaken for Leiner's disease—and this would, of course, not prove any relationship of either of these to seborrheic dermatitis.

Clinical Description, Course and Complications

The initial phase of atopic dermatitis in infants can be described as a diffuse inflammatory infiltration of a large area of the skin which causes an intense sensation of itching from the outset. Therefore one cannot expect to find any definite primary element which might be useful for diagnostic purposes. Onset with the formation of pinhead-sized to lentil-sized exudative papules is exceptional. For this reason these lesions cannot be regarded as the primary efflorescences of atopic dermatitis. By peripheral extension and confluence they are readily transformed into larger eczematoid, later lichenified, patches.

Gradually the infiltration increases; the patches may or may not spread peripherally. They are pink or bright red and have irregular but sharply outlined borders. The surface is at first smooth, is neither vesicular nor moist and is not covered with scales or crusts. The patches are often not elevated above the surrounding skin, and palpation does not reveal any difference between these lesions and the normal skin. At a later phase branlike scaling may be seen, and subsequent lichenification may be observed in severe, long, drawn-out cases under observation for a long period. But lichenification is exceptional during infancy. (I remember only one case of widespread atopic dermatitis in an infant of 11 months in which the face showed slight, but definite, lichenification.) Owing to the loss of elasticity of the inflamed skin, superficial cracks may be found around the mouth, at the angles of the eyes, behind the ears and in the creases of the arms and legs.

The fact that lichenification is absent during infancy has retarded the pediatrician's acceptance of the concept of atopic dermatitis as a morbid entity. However, as Sulzberger and his school have emphasized, there is ample evidence of the identity of the nonlichenified eruptions in the infant with the lichenified patches of atopic dermatitis in children beyond infancy and in adults. This identity was already recognized fundamentally many years ago: The symmetric involvement of sites of predilection (face, antecubital and popliteal spaces, groin and neck) and the unbearable itching support the diagnosis of atopic dermatitis in infants. The face is almost always involved first, whereas it is less frequently a site of the dermatitis in older children and adults. If other typical sites, particularly the antecubital and popliteal spaces, are also involved the diagnosis of atopic dermatitis can be regarded as established.

Often, however, the rash shows on the face alone or on the face and scalp. I believe there is now ample proof that in these cases the same pathogenic mechanism is operative as in the disseminated ones, and that the concept of atopic dermatitis would be incomplete if these cases were to be excluded and placed in any other class of dermatoses.

The initial phase of atopic dermatitis on the face in infancy can be described as a symmetric, slightly erythematous dermatitis in the center of both cheeks. It may be so insignificant as to be overlooked by the parents unless itching, scratching or rubbing of the face on the pillow makes it evident. Soon, roughness of the skin and a fine scaling may appear. If the dermatitis spreads peripherally it may cover the entire face, but usually the chin, the circumoral area and the skin around the eyes are not affected. Claims that atopic dermatitis on the face of infants begins with a papulovesicular eruption are based on incorrect observations. It becomes vesicular by secondary eczematization, which may complicate it right after its appearance.

Very commonly there is a coincident erythematosquamous, psoriasiform rash on the hairy scalp, which is readily mistaken for seborrheic dermatitis. Discoid, sharply outlined red plaques with lamellar scales cover large parts of the entire scalp. This may be preceded by a more or less pronounced dry desquamation almost identical with seborrhea sicca, except for the intense sensation of itching. This eruption of the scalp is sometimes the first sign of atopic dermatitis in the in-

fant; it then descends occasionally onto the forehead and farther down over the face.

Rounded, oval, discoid, sharply outlined plaques of coin size, usually covered with flaky scales but sometimes displaying more exudative surfaces, may also present themselves on the skin of the trunk and extremities, not only on the flexor surfaces but on the extensor aspects as well. In adults, identical discoid lesions are sometimes held to be representative of "nummular eczema," "infectious eczematoid dermatitis" and "seborrheic dermatitis." In my experience they must be regarded as symptoms of atopic dermatitis in infants and in children beyond infancy.

The picture would be incomplete, however, if secondary eczematization were not to be mentioned as a very frequent complication of atopic dermatitis in infancy. One can say without exaggeration that almost every case of atopic dermatitis in infancy and also in childhood beyond infancy has for some time the character of a more acute inflammatory dermatitis, with a pronounced tendency toward vesiculation, edema, oozing and the formation of crusts. This is particularly frequent on the face and scalp in infants. It must now be realized that these symptoms do not belong to the typical picture of atopic dermatitis but are to be regarded as complications. This conclusion seems to be the logical one from everyday observations. It is generally recognized that atopic dermatitis must be given a place outside the eczemas because of its different clinical and histologic picture. Eczematization is exceptional in atopic dermatitis of adolescents and adults. If it is to be regarded as a definite complication in psoriasis, dermatomycoses and other noneczematous dermatoses, it must logically be recorded as a complication of atopic dermatitis as well. This is valid also for the infantile form of atopic dermatitis, despite the fact that eczematization is so common in infancy. It should be recalled that as early as in 1905 Czerny interpreted "eczema" on the face of infants as a complication of what he termed "crusta lactea," a dry, erythematous or erythematosquamous, nonvesicular dermatitis; and that, according to Moro, long before this Bednar had recognized a dry phase preceding exudative "eczema" on the face, which he called "pityriasis rubra faciei." Moro designated this first, dry eruption as "dermatitis erythematosa seborrhoides larvalis lactentium." It is obvious today that all these writers had the first or primary stage of atopic dermatitis in mind.

The grouping of eczematized atopic dermatitis with "ordinary eczema" (allergic eczematous contact-type dermatitis) had been largely retained although, much earlier than Czerny, such an excellent clinician and critical observer as Brocq[6] had set up a particular type of neurodermatitis for this eczematous complication of atopic dermatitis. His "névrodermite multiforme à forme objective eczémato-lichénienne" must be interpreted in our terms as atopic dermatitis complicated by eczematization.

The meaning of the term "eczematization" has changed since it was introduced by Besnier.[7] It has been restricted by Jadassohn,[8] Sulzberger[9] and others to the designation of an eczematous dermatitis engrafted upon and complicating a noneczematous skin eruption. The conception of eczematization by Besnier was originally in line with the ideas of Besnier's time. It was then used to designate an acute eczematous contact-type dermatitis on a skin without the "constitutional" background of eczema (eczématose; eczéma maladie). When it became clear that there is no fundamental difference between contact dermatitis (primary eczematization) and eczématose, it was suggested that the expression be reserved for a secondary phenomenon: the eruption of an eczematous dermatitis as a *complication of a pre-existing* noneczematous dermatosis. Such an eczematization may be due to an eczematogenic allergen coming in contact with the skin from without. Well known causes of eczematization in atopic dermatitis in infants are, for instance, local remedies used for its treatment (tars, salicylic acid, ammoniated mercury, resorcinol, etc.), cosmetics, and chemicals in clothing. In these instances positive reactions to patch tests may provide valid proof of the eczematogenic allergen.

Contacts with an external allergen, how-

ever, cannot be demonstrated as the cause of eczematization in most cases. But whether they are of known or unknown cause, the acute symptoms of eczematization, including vesiculation and oozing, are generally transitory. They usually disappear when treated with mild antieczematous applications, and the stubborn, dry, scaling, original eruption of atopic dermatitis remains. Cases in which eczematization resists almost every kind of treatment over a long period are exceptional.

For practical diagnostic and therapeutic considerations it is well to distinguish as clearly as possible between uncomplicated and eczematized atopic dermatitis. Occasionally one has a chance to watch the process of eczematization from the start. A fulminant vesiculation of the previously dry, erythematous, perhaps scaling patch of atopic dermatitis is not exceptional. The beginning of eczematization, however, is often less acute, and is then at first marked solely by a more inflammatory state, with some edema and swelling of the pre-existing lesion. In this phase the original character of atopic dermatitis is still retained to such an extent as to permit the diagnosis.

This eczematized atopic dermatitis is, of course, different from what has recently been termed "exudative neurodermatitis." The localization of this controversial dermatosis is different from that of atopic dermatitis. The extensor surfaces of the extremities and of the hands and feet are mainly involved, whereas the creases and the flexor surfaces remain free.

The frequency of "impetiginization" or "pyodermatization" as a regular complication in eczematized atopic dermatitis (i.e., an invasion of weeping surfaces with pyogenic micro-organisms, etc.) is of the same order as that in cases of primary contact-type eczematous dermatitis. Another complication, Kaposi's varicelliform eruption (pustulosis vacciniformis), is quite generally due to an infection of the eczematized areas with the virus of herpes simplex and manifests itself by a dense papulovesicular and pustular rash, the vesicles being umbilicated. It is seen most often on the face but may involve other areas of the skin; it develops suddenly and is accompanied by high fever and general malaise.

In recent papers it is suggested that the diagnosis of atopic dermatitis in infants and in children beyond infancy should be based on the performance of skin tests for allergic reactions.[9-12] This is recommended by writers who find it difficult to rule out other eczematoid eruptions from a purely morphologic, clinical point of view. Such reliance on the laboratory, however, is unrealistic and fallacious. It is in some way a consequence of the confused classification of eczematoid eruptions in infancy, particularly of misconceived differentiation of atopic dermatitis and seborrheic dermatitis. If the concept of atopic dermatitis is reinstated to its legitimate position, corresponding to the former "diathetic eczema" in infants, the diagnosis can be established in the simplest way without an elaborate skin-testing procedure, the results of which have little practical value in individual cases.

Management

Extensive experience with the treatment of atopic dermatitis has led me to stress the significance of a correct local treatment of the skin ailment as the very foundation of therapy in every case. This treatment is, of necessity, symptomatic and therefore has its limitations. Despite this reservation the results are usually very satisfactory even in the most persistent cases if the physician has the ability to cope with the individual problems of the patient. It is of little use to have only one or two standard remedies at hand to be used in every case. It requires knowledge, critical appraisal and imagination to apply the right remedy, at the right time, in the right place. The local use of crude coal tar preparations, still the most valuable part of our armamentarium, must be instituted with great care. Undiluted crude coal tar and 5 per cent crude coal tar ointment U.S.P. are useful but not always well tolerated. Coal tar solution N.F. (liquor carbonis detergens) is preferable, especially in modified Neisser's shake lotion (3 to 10 per cent) (see ℞ 1). For many years I have found the addition of 10 per cent liquid CALMITOL® to this lotion convenient in

combating the itching. The formula, then, reads as follows:

℞ 1
Liquid calmitol 10.0
Coal tar solution N.F. 3.0-10.0
Zinc oxide,
Starch,
Glycerin āā 17.0
Distilled water, in sufficient quantity
To make 100.0
Directions: Apply three times a day.

This lotion works very well on the dry, scaling patches on the extremities, the trunk and the neck, and is in general better tolerated than ointments, especially those made up with petrolatum or hydrous wool fat (lanolin) as the base. On the face, the following ointment may be substituted for the lotion:

℞ 2
Liquid calmitol 10.0
Coal tar solution N.F. ..... 1.0 to 3.0 or more
Zinc oxide 10.0
Distilled water 20.0
Ar-Ex multibase, in sufficient quantity
To make 100.0
Directions: Apply three times daily.

Use of this ointment is also indicated for other areas of the bare skin (up to 10 per cent of coal tar solution N.F.) if practical experience shows that the lotion dries the skin uncomfortably.

Addition of 1 to 4 per cent of resorcinol to the lotion may enhance its effect. If the skin is improved, an application of undiluted coal tar solution N.F. or of undiluted crude coal tar may do better than the strongest lotion. The application should be made once or twice a day. Excellent results are often obtained by a combination of the tar with ultraviolet radiation (see later). Other tar derivatives are occasionally as good as or even better than the coal tar solution N.F. I have made use of SUPERTAH® ointment, 5 and 10 per cent (Tailby Nason) and ZETAR® concentrate (colloidal crude coal tar, Dermik Pharmacal Company) and have found them valuable. Wood tars like juniper tar N.F. (oleum cadini) and rectified birch tar oil N.F. (oleum rusci) are less reliable, but I have occasionally seen good results from the Viennese tar tincture in extremely resistant residues. Its formula is as follows:

℞ 3
Rectified birch tar oil 50.0-70.0
Alcohol, U.S.P.,
Ether, each in sufficient quantity
To make 100.0

Also, the old French balsam of Duret (baume du Docteur Baissade) in the modification by Jadassohn (a combination of coal and wood tar with sulfur) has proved efficacious in my experience.* It is added to plain Lassar's paste U.S.P. (zinc oxide paste) 0.5 per cent to 5 per cent. PRAGMATAR® ointment (Smith, Kline and French Laboratories) contains a similar combination, but the disadvantage of such a proprietary item is that it has a fixed formula and cannot be individualized.

Wherever eczematization occurs, one must rely first of all on milder remedies. Zinc oxide paste U.S.P. with eventually small, gradually increased amounts of coal tar solution N.F. (0.5 to 2 per cent or more) and 10 per cent liquid calmitol usually works out very well. It is necessary to cover the paste with a liberal layer of sterile gauze and to bandage (for the face mask made of linen, see Sulzberger[13]). In eruptions with considerable edema and oozing, coal tar preparations should be left out until the eczematization is fairly well under control. ICHTHYOL® 1 to 3 per cent or naphthalan, DERNAFTAN® or NAFTEX®** 5 to 20 per cent may then do better. If the swelling is excessive, zinc oxide and olive oil āā are helpful in combating the edema. Rarely is there a need for wet dressing. Acriflavine 1:3000 is preferable to aluminum subacetate or boric acid solutions. When the swelling is reduced, ichthyol and naphthalan, dernaftan or naftex are replaced by gradually increasing doses of coal tar solution N.F.

Against prevailing impetiginization, plain Lassar's zinc paste with acriflavine 1:1000 (dissolved in water in sufficient quantity and taken up in a minimum of a water-miscible

*Duret's balsam contains 4.5 per cent oleum lithanthracis (crude coal tar), 3.5 per cent juniper tar, 0.5 per cent resorcinol and 3.5 per cent precipitated sulfur, in glycerin, acetone, castor oil and hydrous wool fat.

**Naphthalan substitutes such as dernaftan or naftex seem to be somewhat less efficient than the genuine Russian naphthalan.

base, and then incorporated into the paste), or iodochlorohydroxyquinoline U.S.P. (VIOFORM®) 3 to 10 per cent with calmitol has proved satisfactory. It is well to add to this paste small amounts of coal tar solution N.F. from the beginning and to increase it as soon as it is tolerated by the skin.

Antibiotics are, in my opinion, of limited use. AUREOMYCIN® has proved valuable against Kaposi's varicelliform eruption. Several times I have been impressed with the instantaneous regression of this severe complication when wet dressings with acriflavine solution 1:3000 are applied.

The topical use of antihistaminic drugs may reduce the itching but is, in my opinion, without any other effect on the dermatitis.

It seems advisable to increase gradually the concentration of the tar fraction in lotions or ointments and pastes, especially in the more acute and exudative eruptions, because untoward side effects may be expected when strong concentrations are used in the beginning. In addition, atopic dermatitis in infancy, as a matter of fact, often (but not always) reacts better to mild tar application than it does to stronger ones.

Other topical remedies do not have a dominant place in the treatment of the dermatosis. Instead of calmitol, I have made use of a combination of 0.25 per cent menthol and 2 per cent phenol, but the allergenic and toxic properties of phenol may cause setbacks. The same can be said with regard to ethyl aminobenzoate (benzocaine) 10 per cent and cyclomethycaine (SURFACAINE®) 2 per cent.

A few statements about the proper way in which to clean the diseased skin areas are in order. It is well to replace ordinary soaps with one of the so-called soapless detergents made from sulfated alcohols, such as PHISODERM® and LOWILA®. However, these too are contraindicated in cases of eczematized atopic dermatitis. Light liquid petrolatum U.S.P. or pure petroleum benzin U.S.P. (petroleum ether) is then the proper detergent. Care should be taken to avoid unnecessary rubbing. Crusts must be removed with petroleum benzin U.S.P. when they are sufficiently softened by the grease of the salves. When they are exceedingly heavy they may be washed off with a soapless detergent, but then only once before treatment is started. Residues of ointments and lotions which do not come off easily are left in place and the new coat is applied over them.

On the hairy scalp the following formula has proved to be most satisfactory in my experience:

℞ 4

Ammoniated mercury	1.0
Coal tar solution N.F.	3.0 to 6.0
Benzoinated lard N.F. (or other water-miscible ointment base), in sufficient quantity	
To make	30.0

Directions: Apply to scalp once a day.

Benzoinated lard is still one of the most convenient bases for hairy areas of the skin, because it is readily saponified with water and soap and washed out of the hair. A very light coat of the ointment is sufficient. It should be left on the scalp for 24 hours and washed off with ordinary soap, superfatted soap or sulfated alcohol. As a rule the skin of the scalp is not as sensitive to soaps as the bare skin. When the eruption on the scalp becomes eczematized and impetiginized, soaps must be discontinued and the treatment must rely first of all on the mild antieczematous remedies which are used for oozing and crusted eruptions on the face.

It is exceptional for the rash on the scalp to be resistant to treatment with the above-described ointment. If such is the case, the addition of 5 to 10 per cent salicylic acid, and eventually that of 2 to 4 per cent pyrogallol, proves helpful. One should look out for the possible allergic reactions to the combination of salicylic acid and ammoniated mercury. The substitution of zinc oxide for ammoniated mercury, however, is usually not as satisfactory. The formula of this ointment, then, is as follows:

℞ 5

Salicylic acid	1.5-3.0
Ammoniated mercury (or zinc oxide)	1.0
Pyrogallol	0.6-1.2
Coal tar solution N.F.	6.0
Benzoinated lard, in sufficient quantity	
To make	30.0

Directions: Apply to scalp once a day.

The use of undiluted crude coal tar or undiluted coal tar solution N.F. on the scalp is rarely indicated.

After the eruption on the scalp is completely healed, it is well to use an alcoholic solution of 1 per cent salicylic acid once a day for the prevention of recurrences.

Excellent results in the treatment of all forms of atopic dermatitis in infancy are obtained with radiotherapy. Since Jadassohn[14] recommended x-rays for the treatment of infantile atopic dermatitis, they have been widely accepted as one of the best therapeutic means in resistant cases. A dose of 30 r is safe and efficient. With oil-immersed tubes, unfiltered rays 70 to 80 peak kilovolts should be used. On the face one or two fields may be treated; on the scalp, two to four. The focal skin distance should be 10 to 12 inches (25 to 30 cm.). Three or four treatments in a 10 day interval usually lead to complete regression. When properly administered by qualified dermatologists or other physicians experienced in the superficial irradiation of skin diseases, no harmful aftereffects occur. Nevertheless it should be a general rule that x-rays should be applied only when other methods have been unsatisfactory.

Grenz rays also are of great help in most cases and are entirely safe in qualified dermatologic hands.

Thorium X is also extremely valuable and safe. I prefer a solution of thorium X in isopropyl alcohol, containing 150 millicuries (1000 electrostatic units) per cubic centimeter. Five coats are applied to the area and covered with a rosin solution (VULNOFIX®—Standard Pharmaceutical Company). After two days it must be thoroughly removed with a solvent, preferably pure petroleum benzin. Its use is followed by a slight erythematous reaction, which should not be confused with the erythema due to an overdose of x-rays. After it subsides, pigmentation is left for a few weeks. No harmful side effects or aftereffects have ever been observed. Because of its superficial irradiation, thorium X can be applied as often as it is needed. An interval of four weeks between the treatments is proper, for after this length of time the final effect of the previous course of treatment can be appraised more accurately.*

Very good results are also obtained with a combination of ultraviolet radiation and a local application of coal tar solution N.F. (Sulzberger). Whenever it is possible, the entire skin should be exposed to increasing amounts of ultraviolet rays twice a week while the tar solution is applied locally to the diseased skin areas.

It should be emphasized that as a general rule systemic treatment should not be the primary consideration when the local treatment of the kind outlined leads to satisfactory results and no obvious deficiencies can be detected. The correction of maladjustments in the patient's general health is, of course, imperative. Overfed, pasty infants benefit from a reduced intake of liquid and a diet rich in protein. This counteracts particularly the patient's tendency toward eczematization but it cannot be suspected of having any influence on the underlying atopic dermatitis. General ultraviolet irradiation is very effective against eventual psychosomatic sequelae. A fully balanced diet with the proper vitamins is equally important.

The correction of the state of allergy should be tried in a purely empiric way, because the results of skin tests are often without any significance. If a food is suspected on the basis of a careful history or of observations by an intelligent mother, proof may be obtained by the practical test of repeated, complete elimination and re-exposure. During the first year of life, cow's milk and wheat can easily be substituted by soybean preparations or goat's milk, and oat meal or corn meal. Egg white should be avoided. Attention should also be paid to a possible allergy to fish oils in vitamins. Synthetic vitamins may be used. One should not stick to an elimination diet for an unreasonably long time, and

*Thorium X is a crystalline substance of the thorium group, a direct product of the dissociation of radiothor. Ninety-nine per cent of its radiation consists of alpha rays, i.e., positively charged helium nuclei, the absorption of which causes a strictly superficial effect. The fundamental difference between this superficial irradiation and that of x-rays or radium is that the alpha rays do not penetrate into the deeper layers of the skin. The radioactivity of thorium X is short-lived. Its "half-life" (time of half-decay) is 3.64 days. Therefore, *it has to be applied on the date for which it is calibrated.* Thorium X is distributed in the United States by Fleischman, Burd & Company, 22 West 48th Street, New York 19, New York.

dieting should never be directed by aimless experimenting for a long period. It should always be guided by the principle that the health of the child should not be impaired.

Attention must also be paid to environmental, mainly air-borne, allergens. The elimination of dust, of course, often presents a precarious problem and is usually more difficult than the elimination of foods. However, without proof of a specific kind of dust as the offender, miraculous cures occasionally may be achieved by a simple change of the environment, such as hospitalization or going to a high altitude or the seacoast. (It must be admitted that a change in environment may have mechanisms other than elimination of allergens, but there are old observations supporting strongly the concept of elimination of air-borne allergens.) Unfortunately, relapses usually follow the return to the old environment.

The bedrooms of the affected babies should be kept as free of dust as possible, i.e., no drapes, curtains, upholstered furniture, rugs, stuffed toys or feather pillows. Venetian blinds, linoleum floor coverings, and allergen-proof covers for mattresses and pillows should be used.

Methods of hyposensitization and desensitization are not yet on a safe or effective basis. Nonspecific desensitization is achieved to some extent by the ordinary methods of local treatment, a fact which was long ago referred to, particularly by Lewandowsky.[15] The use of antihistamines by mouth is often helpful if it cuts down the sensation of itching efficiently. Chlorcyclizine hydrochloride (PERAZIL®) tripelennamine (PYRIBENZAMINE®) and, more recently, a new synthetic antihistamine derived from phenothiazine (PHENERGAN®) taken by mouth have proved of value in my experience. It is difficult to decide whether or not they fundamentally influence the dermatitis. They should be omitted as soon as it becomes clear that they do not benefit the patient, or as soon as side effects appear. This implies that the pharmacist should not be permitted to dispense them again without a new prescription.

I have not yet had occasion or opportunity to evaluate cortisone or ACTH in atopic dermatitis of infancy.

Summary

The former "diathetic" or "constitutional" eczema in the infant corresponds to the infantile form of atopic dermatitis and represents a definite morbid entity. It must be identified with the former "neurodermatitis disseminata" or disseminated lichen simplex. The modern classification and concepts of atopic dermatitis are on a broader and more rational basis than older designations.

During infancy the absence of lichenification presents delicate problems in diagnosis, and the frequent eczematization may lead to confusion with eczematous eruptions. The significance of these features is discussed, and an attempt is made to define eczematization in atopic dermatitis more precisely.

Correct topical treatment of the skin is still fundamental in atopic dermatitis. Crude coal tar preparations, ultraviolet rays, x-rays, Grenz rays and thorium X must be used intelligently and are then generally effective and always safe.

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GENERAL PRACTICE *Review*

This department offers the latest, proved methods for the treatment and management of commonly encountered conditions based on the extensive experience of the physicians who prepare these summaries for POSTGRADUATE MEDICINE.

Acute and Chronic Pancreatitis

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In spite of much investigation and thoughtful study, the etiology of both acute and chronic forms of pancreatitis is still obscure and controversial. For an excellent review of this subject the reader is referred to a recent publication by Ivy and Gibbs.[1] In summary it may be stated that both acute and chronic pancreatitis can be caused by obstruction of the pancreatic duct, by interference of the blood supply to the pancreas, and by the lodging of infectious agents in the organ by way of the blood vessels, lymphatics or by material refluxed into the pancreatic ductal system. Probably in many cases more than one mechanism is involved.

The clinician is presented with three main forms of pancreatitis—(1) acute hemorrhagic pancreatitis, (2) acute pancreatic edema and (3) chronic relapsing pancreatitis.

Acute Hemorrhagic Pancreatitis

This is usually a violent and often a fatal disease, and has been recognized by surgeons for many years. In common with all forms of pancreatitis, it is most difficult to diagnose accurately from the presenting symptoms and physical signs, which may mimic almost any acute abdominal crisis. It is relatively rare for the diagnosis to be made preoperatively (in the absence of operation it only can be definitely determined by postmortem findings or by reason of its late complications).

The patient in a classic case usually is stricken suddenly, often after a heavy meal or a drinking bout, with epigastric pain. Shock often is present early, and the other findings said to be suggestive are the relatively fast pulse, low temperature and predominance of tenderness in proportion to the degree of abdominal spasm. Some writers have mentioned an early bluish mottled appearance of the skin; this is probably due to the degree of shock. Vomiting is usually not intense or prolonged. Sometimes the pain is referred to the anatomic level of the pancreas in the high lumbar or low thoracic level, but this is not nearly as characteristic of the acute disease as of the chronic disorders of the pancreas. The patient is often thought to have acute perforation of a peptic ulcer, coronary thrombosis, intestinal obstruction, cholelithiasis or cholecystitis, or more often perhaps, mesen-

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teric thrombosis. Since gallbladder disease is so often associated with pancreatitis, the diagnosis is especially confusing in the presence of jaundice, which occurs in about 15 per cent of attacks of acute pancreatitis.

There is usually marked leukocytosis with neutrophils predominating. The blood sugar is often elevated because of suppression of the islet cells. The one laboratory procedure of supreme importance is the serum amylase test. In the first 24 to 48 hours of the acute phase it is almost always markedly elevated. The serum lipase tends to rise later and to remain elevated longer. Because of this the test will be most helpful when the patient presents himself some days after the onset of symptoms. In severe cases the blood calcium drops to rather low levels and thus is helpful both in tending to confirm the diagnosis and in judging the prognosis. It is stated that a serum calcium level of less than 7 mg. per cent is almost uniformly associated with a fatal outcome.

Perforated peptic ulcer usually may be excluded by the absence of free air in x-rays of the abdomen, especially if several positions are used, including the lateral decubitus. An electrocardiogram should be taken to exclude an obvious coronary occlusion. However, the presence of minor variations in the tracings may confuse the issue, by reason of reflex coronary artery spasm due to the pain and shock, and changes in the serum electrolytes.

The complications of acute pancreatitis are pancreatic abscess, cyst formation, pancreatic fistulas, pancreatic fibrosis, and atrophy. Cholecystitis and cholelithiasis also may be true sequelae. The disease may progress to chronic relapsing pancreatitis, with or without steatorrhea and diabetes. The Grey Turner sign is a discoloration seen in the flanks, and sometimes seen as far forward as Poupart's ligament and the umbilicus, caused by extravasation of the products of enzymatic digestion into the extraperitoneal spaces.

Surgical management—It is the consensus that immediate operation is undesirable if one is sure of the diagnosis. The diagnosis is not made preoperatively as often as it is missed. If the abdomen is opened because of the suspicion of some other grave abdominal emergency, such as perforation of a peptic ulcer, it is advisable to do as little as possible. The highly charged enzymatic fluids can be removed and drainage provided for their reaccumulation; if there is obvious disease of the biliary system a cholecystostomy or cholecystectomy with T tube drainage is indicated. Some surgeons insist that, even in the absence of gallbladder disease, biliary decompression is advisable because of its favorable effect on relief of pancreatic duct pressure. On theoretical grounds it seems doubtful that such a procedure is sound, yet the clinical experience of many able surgeons seems to show that it is of practical value. If possible, the healthy gallbladder should not be removed; it may be of vital importance to the patient to have it available for a later bypass if the cicatricial tissue from the pancreatic inflammation obstructs the ampulla or the common duct.

Diagnostic and therapeutic paracentesis is advocated by some surgeons. The fluid so obtained will be found to have very high amylase and trypsin values.

Operation is imperative when, in the course of the disease, signs of continuing visceral digestion, pancreatic abscess, cyst formation or filling of the lesser omental sac are suspected. The Grey Turner sign is useful in the latter case.

Conservative measures—In the acute phase nothing should be given by mouth. Gastric suction should be maintained, not only because of its decompressing value to forestall ileus, but also because gastric acid tends to cause spasm of the sphincter of Oddi and of the duodenal wall, thus increasing intrapancreatic pressure. Acid also sets off the secretin mechanism, which stimulates the acinar cells of the pancreas to produce even more autodigestive juice and raise the intraductal pressure in an already obstructed gland. (Rupture of the acini occurs probably at pressures around 300 mm. of water.) Intravenous fluids are therefore a necessity for the critical phase of the illness.

If the blood sugar is higher than one would discount from the glucose which is given intravenously, insulin will be necessary, both to

make use of the injected sugar and to prevent exhaustion of the beta cells of the islets which would make temporary diabetes permanent. Calcium should be given intravenously if there is a demonstrable fall to low levels in the course of the disease. Because it has been shown that the vagus exercises a tonic effect on the pancreatic acinar cells, causing a richer and greater secretion of pancreatic juice than when there has been a vagotomy, drugs such as atropine and BANTHINE® are theoretically sound. Morphine, having a spastic effect on the sphincter of Oddi, should be withheld if possible, and DEMEROL® used in its place if barbiturates do not control the pain. Because the pancreas produces an antitryptic factor normally, this may be absent in acute inflammation, and this is thought to be the reason why a hemorrhagic diathesis develops in acute pancreatitis. Extracts from soybean flour are rich in such antitryptic factors. When these become commercially available they may prove to be of benefit in lessening the acute pancreatic hemorrhage itself and in preventing late hemorrhages.

How long should one deprive the patient of water and fluid by mouth? This question cannot be answered categorically but must be left to the physician's judgment in assessing the decline of the acute inflammatory phase by the lessening of pain, distention and fever; by the return of pulse and blood pressure to normal, and by the general appearance of the patient. I know of no sure laboratory guides in making this decision.

Antibiotics should be given from the beginning. In the absence of any proved infectious agent penicillin in doses up to 1,200,000 units a day is probably the safest drug to use.

Despite the best of care, the mortality rate in severe hemorrhagic pancreatitis is about 50 per cent. It is higher in those patients operated on early in the disease than in those whose operation has been delayed until a complication is manifest. Nevertheless it is not right to place blame of this high mortality rate on premature operation, because there is usually reasonable doubt of the accuracy of the diagnosis, and the possibility exists that one may miss the chance to repair a perforated ulcer, or resect a gangrenous loop of bowel by prompt exploration.

Acute Pancreatic Edema

By definition this is an acute form of pancreatitis in which there is a suddenly developing inflammation which does not go on to hemorrhage and necrosis. The symptoms and physical findings are essentially the same but are usually less severe than in the hemorrhagic form and the patient does not seem as critically ill. Jaundice is not infrequent. It is probably due to pressure on, or actual inflammation of, the terminal common bile duct, or to a pancreatic calculus at the ampulla. It seems probable that persons can have successive attacks of either form of acute pancreatitis, and that pancreatic edema can either follow or precede attacks of pancreatic necrosis over the course of years.

The diagnosis of pancreatic edema is important because operation is not necessary. The one test of greatest value in this situation, and without which the diagnosis is speculative, is again the serum amylase elevation during the early phase of the disease. The conservative measures outlined for the treatment of acute hemorrhagic pancreatitis are suggested for the management of this milder form of acute pancreatitis.

Chronic Pancreatitis

Chronic pancreatitis may be present to the extent of almost complete atrophy, extensive calcification or severe fibrosis without giving rise to symptoms. From this silent form it runs the gamut to attacks of severe, recurring pain sufficient to cause addiction to narcotics or alcohol, and to a severe malnutrition due to loss of fats, minerals and proteins in the stools. The degree of damage to the pancreas seems at times to be perversely at variance with the symptoms and manifestations. With the realization that few patients present all of the manifestations which will be listed, we shall proceed with some of the features presented by this disease.

Pain—When all other commoner causes of chronic or recurrent abdominal pain are ruled out, one should suspect pancreatitis especially

when (1) the pain is in the upper abdomen (right, left or midline) and radiates to the spine or flanks in the same cross section level of the trunk, rather than midscapular or lumbar level; (2) the worst pain comes after excessive use of alcohol, or about one to two hours after meals, or is absent if the patient fasts, and especially if food does not relieve pain already present; (3) tenderness cannot be found on physical examination to correspond with the degree of pain; (4) the patient is suspected of being psychoneurotic, having been free from such traits until the development of pain, and (5) the syndrome follows an episode of acute pancreatitis.

Steatorrhea—This may be present in gross form, as a diarrhea of bulky, greasy stools, or may be absent entirely (as reported after surgical removal of the whole pancreas) or be detectable only by quantitative chemical tests. In severe cases up to 80 per cent of the ingested fat may be lost to the patient. Associated with this is the loss of fat-soluble vitamins. The condition must be distinguished from the sprue syndrome (idiopathic steatorrhea), chronic enteritis of all sorts, ulcerative ileocolitis, and fat losses following such surgical procedures as gastrectomy and short-circuiting operations of the bowel, and from that very rare disease, Whipple's intestinal lipodystrophy.

Diabetes—A certain percentage of patients will acquire diabetes following acute, subacute or chronic disease of the pancreas, due to destruction of the islets by acute inflammation or by strangulation fibrosis. The diabetes is usually characterized by the term "labile" and is difficult to control. If enough insulin is given to reduce the blood sugar to normal and to keep the urine reasonably sugar-free, the patients tend to have frequent attacks of insulin shock.

Calcification of the pancreas—This may consist, less commonly, of pancreatic calculi, either single or multiple, or of diffuse calcification of the gland. Calcification may be limited to part of the organ or be widespread. It is said to develop at times within a few months of the original attack. In one of our patients it took 16 years to manifest itself and appeared as a full blown parenchymal calcification between the sixteenth and seventeenth year of the illness. Calcification of the pancreas, in the absence of general visceral calcification, is the hallmark of chronic inflammatory disease of the pancreas.

Diagnostic aids—When abdominal pain, fatty stools, diabetes and calcification of the pancreas are present in a patient, there is little need to use laboratory aids to confirm the diagnosis. The finding of gross fat and undigested muscle fibers in the stool gives a lead to the diagnosis, as does glycosuria, although the absence of these findings by no means excludes pancreatitis. It is now conceded that quantitative determinations of stool fat and nitrogen and the ratio of fats to fatty acids, while of interest, are not conclusive enough to distinguish pancreatic steatorrhea from other types of fat loss. Special tests which aid in the diagnosis of chronic pancreatitis are listed here in the approximate order of their availability and simplicity:

1. Film of the abdomen for signs of calcification.

2. Oral glucose tolerance test (flat in sprue; normal or of diabetic type in pancreatitis).

3. Roentgenographic studies of the duodenal loop to determine anatomic distortion of the pancreas.

4. Serum amylase determination, done early in an attack of recurrent pain, or serially over several months (elevation or marked variation suggests pancreatitis).

5. Serum amylase and lipase test using secretin stimulation.[2] Gross elevations over fasting levels are highly suggestive but are found in other diseases at times, notably liver disease.

6. Vitamin A tolerance test (low in both pancreatitis and sprue if standard preparations are used; normal in pancreatitis and low in sprue, if the alcohol-soluble preparation is used).

7. Duodenal intubation for assays of volume, bicarbonate and enzyme content of the pancreatic juice before and after stimulation with secretin.[3]

8. Determination of serum trypsin and the

antitryptic factor are not standardized as yet in most centers. The predominance of serum trypsin may be responsible, as mentioned, for severe gastrointestinal hemorrhages, which have hitherto been poorly understood. These are not uncommon in the course of chronic relapsing pancreatitis—in some series the incidence is as high as 25 to 30 per cent.

Management of Chronic Pancreatitis

Medical management—General measures, which should be insisted upon, concern the prevention of attacks of pain and inflammation and the preservation of viable tissue. The most important of these is the prohibition of alcohol. Several small meals are advisable rather than one or two large meals a day. Diets should be high in protein and low in fat content. At times complete fasting may abort an attack.

Pancreatin is necessary for those patients who have steatorrhea and creatorrhea. It should be given in large doses, up to 10 gm. three times daily. Enteric-coated granules of pancreatin are available and are preferable, although some recent evidence suggests that dogs utilize both forms equally well in the same dosage. Pancreatin in large doses provides a useful diagnostic therapeutic test for establishing the presence of chronic pancreatitis. It also has a lipotropic effect which prevents fatty infiltration of the liver, so often seen in pancreatic disease or after removal of the whole organ. As replacement therapy it provides the pancreatic enzymes necessary for fat, carbohydrate and protein digestion, but only if given in adequate doses.

Drugs are of limited use in the treatment of pain. Banthine is currently popular and there is good scientific basis for its use, as there is for any drug which suppresses vagal stimulation and tends to reduce secretory pressure in the organ. Morphine should be avoided, for the reasons mentioned previously and because addiction is so easily acquired by these patients. Indeed, narcotic addiction is an ever present problem and justifies radical surgical treatment. Nitroglycerin may be useful in relieving the pain, especially pain caused by spasm of the ampulla of Vater.

The diabetes is often troublesome and much patience is required to manage it. It is probably better to make some compromise with perfection of control and to risk occasional glycosuria in the interest of better caloric intake and the avoidance of hypoglycemic shock. The latter theoretically can cause hypersecretion of gastric acid and secondarily stimulate pancreatic secretion. It must also be remembered that when pancreatin is given to a patient, the resulting increase in food absorption will probably increase the insulin needs of the patient.

Surgical management—At the present time opinions of leading surgical clinics are so varied and changing as to the radical treatment of chronic pancreatitis, that one hesitates to do more than enumerate the many operations being performed. In general, surgical treatment has been reserved for those patients with severe pain who have not responded to medical management and for those who have associated disease of the biliary system.

Some Procedures Recommended by Various Authors

Cholecystostomy with drainage
Cholecystectomy with T tube drainage
Choledochoduodenostomy
Roux Y anastomosis
Sphincterotomy of ampulla
Gastrectomy—subtotal
Pancreatectomy—partial or complete
Pancreatolithotomy
Ligation of the pancreatic ducts
Sympathectomy—unilateral or bilateral
Splanchnicectomy—with or without sympathectomy
Vagotomy
Vagotomy and sympathectomy

The degree of success achieved by any of these measures will depend on whether the factors responsible for causing the pain are suppressed. Time will have to show which procedures have given lasting benefit. Since the disease tends to limit itself in some patients by progressive destruction of functioning glandular tissue, patients and their surgeons may be misled into attributing improvement in symptoms to the last measure employed.

Yet when one is faced with a patient who is deteriorating morally and physically from the ravages of the severe forms of this disease, the resort to radical methods is imperative.

In conclusion, inflammatory diseases of the pancreas are difficult to diagnose and to treat successfully, and much remains to be learned about this group of diseases.

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The Antihistamines in Treatment of Allergic Diseases

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During the last few years there have been published several thousand articles dealing with the antihistamines and their use in many of the diseases known to man, ranging from ringworm of the feet to conjunctivitis and from muscle cramps to sunburn. While some of these disease entities are benefited, the major use of the antihistamines is in the symptomatic treatment of allergic diseases. In the search for new, better and different drugs, the pharmaceutic industries have produced so many compounds as to confuse the practitioner. This paper will summarize our experience with some of these drugs in the treatment of allergic diseases, and point out individual differences of a number of them. In an article of this length it will not be possible, of course, to discuss all the compounds manufactured.†

Pharmacology

The chief action of the antihistaminic drugs is to prevent released histamine from reaching the receptor cell by competing with histamine at its site of action. The antihistamines prevent histamine shock in animals, inhibit the asthma from histamine aerosols in guinea pigs, and prevent the contraction of smooth muscle from histamine added in vitro. These drugs also prevent anaphylactic shock. In man they inhibit the wheal and flare normally produced when histamine is placed on the scratched skin or is injected intradermally. The allergic reaction as seen on the skin can be diminished by the local or systemic use of these drugs. The antihistamines are local anesthetics. In animals these compounds produce excitation and in still larger doses convulsions and death. In man the nervous system effect is usually sedation. Some of these drugs, however, are excitatory, and in some people excitation results with those drugs that are usually sedative. With large toxic doses a stage of excitation with muscle irritability results which may finally terminate in convulsions. It has been claimed that some of these drugs diminish capillary permeability.

Treatment of Respiratory Allergy

Results in the treatment of hay fever and allergic rhinitis with the antihistamines have been generally good. Patients with mild

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†For a complete discussion of all these drugs, their pharmacologic and clinical actions and their toxicities, see Feinberg, S. M., Malkiel, S. and Feinberg, A. R.: The Antihistamines. Chicago, The Year Book Publishers, Inc., 1950.

symptoms respond well, but those with severe hay fever very often are only slightly benefited. Nasal stuffiness is much more resistant to the action of these drugs than is the sneezing or rhinorrhea. The mild case of ragweed hay fever responds well to the antihistamines, while in the moderate or severe case the best results are achieved by desensitization, with the additional use of antihistamines when required. Sound allergic management of the patient must be carried out despite the beneficial effects of the drugs. Complete relief is not common with the antihistamines; however, complete relief is the usual result in a patient whose offending allergen is determined by history and testing and can be removed from the environment.

Variability of exposure to the allergen is a factor that must always be included in evaluating the results of any form of treatment. Any antihistamine, vitamin or placebo given during the last few days of the ragweed season will seem to give relief. Exposure to allergens also varies from day to day and from year to year.

Asthma responds poorly to antihistamine medication. The best results usually occur in children; this may be due to the antispasmodic and sedative action of the drugs rather than to their antihistaminic action. At times the antihistamines seem to aggravate the asthma, possibly due to their drying effect. In severe cases antihistamines in aerosol form or given parenterally may be of benefit but usually other drugs, such as ephedrine, epinephrine and aminophylline, are of greater value. Because of the usual lack of effect of the antihistamines in asthma it has been common for us to see patients whose allergy has progressed to asthma although their hay fever has been relieved for a few years with the use of antihistamines only. If desensitization had been employed along with the use of an antihistamine when required this would have been prevented in most of these patients. The allergic cough, often the forerunner of asthma, is more often helped by these drugs.

Dermatologic Allergy

This group of allergic diseases includes urticaria and angioneurotic edema, atopic dermatitis and contact dermatitis. Urticaria and angioneurotic edema are usually improved by the use of the antihistamines. The itching is frequently relieved although the swellings or inflammation may be uninfluenced. In some instances the dose must be raised to rather high levels. Very often one of the drugs will work where others have not. However, better results are achieved if the cause is found and removed. The response of atopic dermatitis to the antihistamines varies. The drugs are frequently of aid in reducing the pruritus characteristic of the disease. In generalized cases oral use is recommended, and frequently one of the sedating drugs is best. Localized areas, if not in the acute weeping or vesicular stage, often may be treated best with an antihistamine ointment, providing it is not too irritating. It is wise to try the drug on a very small area first to make sure that the preparation does not cause inflammation of the patient's skin.

These drugs are helpful in only some instances of contact dermatitis; the most that can be accomplished is relief of the pruritus. Removal of the offending irritant is again of the greatest importance.

Miscellaneous Allergy

Serum sickness and the serum-sickness type of reaction frequently resulting from penicillin and other antibiotics are often benefited greatly by these drugs. The medication must be continued for the duration of the disease; it does not shorten the actual course but will usually relieve the itching and some of the swelling. Recent claims that the addition of an antihistamine to penicillin will prevent the delayed penicillin reaction are neither accurate nor rational. The antihistamine at the time of injection cannot have an effect on the reaction days hence. As a matter of fact, a dose of such a drug is not adequate to prevent a serious immediate reaction from penicillin or any other antigen. Polyarteritis nodosa and the other collagen diseases are benefited little by the antihistamines. Occasionally some symptomatic relief may occur but such drugs as corticotropin and cortisone

are much more effective in these conditions.

Allergic diseases of the eye often respond well to either oral or local use of the antihistamines. Allergic conjunctivitis caused by inhalant allergens and associated with rhinitis may or may not respond satisfactorily to the oral medication; if it does not, the local use of antihistamine eye drops or eye ointment frequently will give the desired effect. Irritation caused by antihistamine eye medications prevents their use in some patients.

Gastrointestinal allergy usually responds poorly to the antihistamines. Taking the drug before the offending food is ingested occasionally will prevent reactions but it is more logical and more satisfactory to eliminate the allergenic food.

TABLE 1

AVERAGE DOSES OF DRUGS USED IN ALLERGIC DISEASES

DRUG	DOSE (MG.) ADULT	CHILD (6 Years)
Antistine	100	50
Benadryl	50	20
Chlorcyclizine	50	25
Chlorothen (tagathen)	50	25
Chlor-trimeton	4	2
Decapryn	25	10
Diatrin	25	10
Histadyl (thenylene)	50	20
Neo-antergan	50	25
Neohetramine	100	50
Phenergan	12.5	6
Pyribenzamine	50	20
Pyrrolazote	50	25
Theophorin	25	10
Trimeton	25	12.5

Drug of Choice

The question, "Which is the best antihistamine?" is asked constantly. An answer to this question is virtually impossible. Different persons respond differently to the various antihistamines. There is a "best" drug for a particular patient under certain conditions. This drug must be determined by the specific needs of the patient and by trial and error. For practical purposes we divide the antihistamines into three or four main groups. If the average physician has a familiarity with one or two drugs in each of these groups he will find himself less confused.

Group 1 comprises the least sedative (and often least potent) drugs, and includes such drugs as ANTISTINE®, NEOHETRAMINE® and THEOPHORIN®. Group 2 contains potent and moderately sedative varieties and includes chlorothen (TAGATHEN®), CHLOR-TRIMETON®, DIATRIN®, diparalene (PERAZIL®), HISTADYL® (THENYLENE®), NEO-ANTERGAN®, PYRIBENZAMINE®, PYRROLAZOTE® and TRIMETON®. Group 3 consists of the potent but highly sedative drugs and comprises drugs such as BENADRYL®, DECAPRYN® and PHENERGAN®. A fourth group would contain the longer-acting drugs such as chlorcyclizine (diparalene and perazil) and phenergan. In choosing the drug the needs of the patient must be considered. For nighttime use or where additional sedation is of benefit a drug from group 3 would be selected. For prolonged action either during the night or under other circumstances where it might be inconvenient to take medication the choice would be from group 4. For the patient easily influenced adversely by sedating drugs we would use a drug from group 1. For general all around use one of the group 2 drugs would be desirable. The average physician will do well to accustom himself to the use of one particular drug from each group. Only in exceptional instances will he need to try more than one drug of a group in the individual patient. Another factor to be considered is that some patients will acquire a tolerance to a specific antihistamine after prolonged use; changing to an alternative drug may solve this problem, at least temporarily.

Doses

The dose depends on several factors. In general it is best to give the smallest amount of the drug that will give relief in a particular case. This may be more or less than the manufacturer's recommendations, as there seems to be great individuality among patients. A larger dose may often be given at night whereas the same amount during the day would not be tolerated because of sedation. The age and size of the patient will, of course,

also determine the amount. Children will often tolerate a higher dose per pound than will adults. Table 1 indicates the average effective doses for an adult and for a child of 6 years. If the symptoms are very severe two or three times the average dose may be required.

Relationship to meals is of great importance, as nearly twice as large a dose is necessary to produce the equivalent effect if taken after meals as compared to the amount given on an empty stomach. The disease treated will have a bearing on the dosage. Side effects, desirable or undesirable, also are a determining factor.

Method of Administration

Oral administration is the most useful route. Parenteral administration is advisable where speed of action is necessary or where oral medication is not retained or absorbed. For example, certain severe cases of serum sickness may respond to parenteral drugs when the oral route has failed or has been unsatisfactory. Topical administration of the antihistaminic drugs in the form of ointments, eye drops or aerosol is indicated in selected cases. A chronic localized pruritic skin lesion will often respond to topical applications. Aerosol administration of certain of the antihistamines is of aid in selected cases of asthma. Variations in the method of oral administration are useful at times. Elixirs and syrups are useful for graduated doses, especially in children. Enteric coating for delayed action is of aid especially during the night, although enteric coating often is unsatisfactory because of irregularity of absorption.

Combinations

Combination of the antihistamine with another drug or with another antihistamine is usually made either for the purpose of counteracting the side effects or for potentiating its action. Occasionally the same drug will do both. Combination with a drug such as ephedrine achieves this latter purpose. Combinations with expectorants and cough depressants are used as cough medicines. There are also combinations with aspirin, caffeine, sedatives, stimulants, aminophylline and so on. The mixture of a short-acting drug with a longer-acting drug has obvious advantages, as some of the long-acting drugs begin their effect an hour or two after ingestion.

Toxic Effects

Minor side effects are frequent. The incidence of severe toxic effects is relatively small but is worthy of consideration. The most common side effect is sedation of varying degree. Stimulation, consisting chiefly of tachycardia, nervousness or insomnia, is also fairly common and the same drug may cause sedation in one person and stimulation in another. Dryness of the mouth is also common. Epigastric distress and nausea are not uncommon and frequently can be eliminated by taking the drug after meals. Other side effects that occur occasionally are urinary retention, dermatitis, hypotension and acute psychosis. Severe reactions and death from extreme overdosage, either by accident or in a suicidal attempt, have been reported. Depression of certain formed blood constituents has occurred rarely after the prolonged use of some of these drugs. The severity and incidence of toxic effects may be reduced by close observation by the physician, proper selection of the drug—mostly by trial and error—and by counteracting the side effects with other appropriate drugs. Allergy to the antihistamines is infrequent but does occur. This is most often a contact type of sensitivity to topical medication or to oral use of the drug.

Summary

A very valuable and basic series of compounds in the form of the antihistamines has been added to the physician's armamentarium in the last few years. The drugs have been shown to be useful in many disease entities and symptoms, being most effective in the treatment of some of the allergic diseases. These drugs have both advantages and disadvantages. There is no one drug that can be said to be the best or most useful. The antihistamines are useful adjuncts, but do not remove the necessity for allergic management in most instances of allergy.

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LAY AGGRESSION IN MEDICAL PRACTICE

We, each of us of this age, are capable experts, on account of our current experiences, on some phase or another of aggression. We have become immune to surprise when someone overruns our national interests. But this immunity has, unfortunately, resulted in an indifference to attack and sloth and lethargy in counterattack. We do not even recognize an aggressor any longer without demanding convincing proof of his aggression. Voices have been raised from time to time threateningly with prophetic warning that we have unlearned our shudder-reaction. Among these warnings, none is more menacing in its significance than the exhortation from our philosophers that we overstress geographic, and woefully understress ideologic aggression.

This threat has a very special meaning for medicine. The people at large have relatively little to gain from physical or material aggression in the medical field, although, even in this way, the false hopes of economic gain may allure certain covetous souls. Payment for the costs of illness through general taxation, controlled by lay administrators, is surely menace enough to stir opposition among the medical profession; but few there are who see what an impending catastrophe is hidden behind lay administration. More menacing is the ideologic aggression by the lay mind. It takes so many forms. The quack wants to secure for himself the honor and trust and, sometimes, the pocketbook that the public gives gladly enough to the competent physician. The medical sectarian who finds it difficult to secure a license from his state attempts to prove the claim of competence by saying that he is every bit as good as a regular doctor. The mildly paranoid layman gloats when he is called "Doctor" or more often "Doc." There are many other forms, too numerous to mention, of this compensatory self-delusion. Somehow, the public craves the various forms of guile which approximate more or less closely these various forms of self-deception.

But illusions or delusions are harmless enough except to the guileless dupe himself. When, however, these forms of delusion are converted into programs of social action, when they take the form, for example, of advertised self-medication or lay control of medical practice, or lay substitution in the administration or the diffusion of medical care, or compulsory governmental control of personnel and equipment, or imposition by law of coercive provisions for future professional, personal or institutional medical care, and so of a hundred other emergents from our present social chaos, these threats cease to be merely spectral. They become as dynamically effective as a gun or dagger in irate, cold-blooded, vicious hands.

The frontal aggression has thus far failed, thank God. Will it triumph in the end? In the meantime, however, there are many flank attacks, burrowings and tunnelings beneath,

and aerial assaults, all coming from different directions at once. Many of these attacks are still in their innocent guise calculated to deceive all except the most wary. The fractionation of medical responsibility by assigning to "assistants," presumably supervised by a physician, parts of an indivisible medical responsibility, the assignment to the medical public relations officer of the doctor's solicitude for maintaining personal and professional relations between himself and his patient, the complaint that no human being can possibly do what today we are demanding of the physician in general practice—all these and many similar implicit and related phenomena are inclusive operations, ideologic rather than material, which, however, are subtly translated into a large variety of demands, all implying some phase of the laicization of medicine. Pleas are becoming eloquent for changes in the curriculum in the school of medicine, with insistence on more and more courses in phases of sociology and economics instead of a deepening of the student's basic science or clinical knowledge; demands for the "enrichment" or, at times, for the "attenuation" of formal requirements for admission; and in some instances, at least, demands for corps of assistants whose manifold and often overlapping and conflicting ministrations render impossible the unified treatment of the patient, and favoring therapeutics not of the human being but of a disease, are but too apt to become routes for lay aggression.

There are several ideologic aggressions against medical practice on the horizon just at this moment. Two might be mentioned: the threat of further governmentalization of medicine through the surreptitious introduction of international agreements and treaties, and the demand for official approval by a professional medical agency, such as a recognized specialty board, of persons competent in one of the basic medical sciences but themselves inexperienced, not being physicians, in the clinical aspects of their respective fields.

It is to the great credit of the American Medical Association that it rose promptly to the defense of medicine as soon as the threat implied in the internationalization of medicine made itself felt. The discussion of "Medical Care and the International Social Security Treaty" in the *Journal of the American Medical Association*, August 23, 1952, page 1574, by Leonard J. Calhoun, is unmistakably clear in pointing out where medicine cannot but be deeply affected adversely in the formulation of policy and the drafting of agreements pertaining to the International Labor Organization Treaty. Similarly, the action of the Council on Medical Education and Hospitals under the Chairmanship of Dr. Herman G. Weiskotten deserves the wholehearted commendation of all those interested in safeguarding the physician's medical responsibility against lay aggression by meeting the threat of a new specialty board in microbiology whose function it would be to recognize not only physicians but also experts in microbiology who do not have their medical degrees.

A word of commendation must also be said to the American Society of Clinical Pathologists which, in its Secretary's Newsletter of July 1952, has analyzed the efforts thus far made to secure approval for nonmedical candidates by the approved medical examining boards in the specialties. It will require not merely the most careful watching but also the most strenuous counteroffensive to combat lay aggression in such fields as these of medical practice.

Horace in one of his epistles says:

> *"Quod medicorum est*
> *Promittunt medici—tractant fabrilia fabri."*
> *"What pertains to the doctors*
> *The doctors manage—craftsmen manage their craft."*

And a line or two further in the same context:

> *"Scribimus indocti doctique poemata passim."*
> *"But all of us, unlearned and learned, write poems now and then";*

or in our context:

> *"But all of us, unlearned and learned, do a little doctoring now and then."*

ALPHONSE M. SCHWITALLA, S.J.

THE PRACTICING PHYSICIAN'S PART IN DRUG RESEARCH

FORTY-ONE years ago, in 1912, I was helping Professor Le Count with postmortem examinations in the Cook County Hospital, Chicago. This was just when coronary thrombosis was discovered. The causes of death in most instances were relatively simple: infections, arteriosclerosis, poisons, gunshot wounds and accidents. Nowadays new knowledge of the mechanism of death enables us to determine causes in many complex cases that would not have been considered then. Study of allergy has brought to light a whole variety of factors that disorder human physiology. The human body apparently has become so complicated by sensitizing influences to which it is exposed, therapeutically or otherwise, that pathologists are not always quite certain as to causes of death.

The evidence seems clear that the use of various medicaments in susceptible persons can cause blood dyscrasias, including aplastic anemia, thrombocytopenic purpura, granulocytopenia and pancytopenia. Moreover, persons may become sensitive to drugs after beginning their use and the factors governing such sensitization differ in various individuals. Food and Drug officials say that the incidence of blood dyscrasias has not increased with the introduction of the new remedies. Yet we recognize that some physicians hesitate to report serious effects. Nevertheless, only the reporting of such unfortunate results can yield an understanding of their incidence and permit the drawing of a balance between the good and harm that new drugs do.

In a recent issue of the *British Medical Journal*, the editor made a casual record of a wide variety of reactions to numerous drugs. For instance, thiouracil, antazoline, PYRIBENZAMINE®, troxidone, methoin, DIPARCOL®, the sulfonamides and aminopyrine may be associated with granulocytosis. The use of troxidone or allylisopropylacetylurea may be followed by thrombocytopenia. Organic arsenicals, sulfonamides, methoin and phenylacetylurea may cause marrow aplasia. Amphetamine and the sulfonamides, especially PROMIN®, may cause hemolytic anemia. Cinchophen, phenylacetylurea and carbon tetrachloride all may cause liver damage. All these potentially toxic drugs, according to the *British Medical Journal*, may be prescribed so freely as to make it impossible to decide which of several actually causes reaction or death in any given case. Discombe has suggested that a standing committee of clinical and forensic pathologists should be set up to collect the facts. He proposes in England a committee to establish a "drug idiosyncrasies registry" which would provide valuable information.

The *Lancet* for October 25 reports that the results with BUTAZOLIDIN® were so favorable that its immediate use started in Great Britain and, in fact, some 100,000 patients had received this drug. Now British writers are reporting that agranulocytosis can be ascribed to butazolidin. The Geigy Company feels that blood counts should be made at least weekly in patients being treated with butazolidin.

In a recent trip to Europe I inquired about reactions to drugs. For instance I inquired in Israel about reactions to drugs in general and particularly to chloramphenicol in the treatment of typhus, typhoid and similar infectious diseases. The physicians in Israel stated that they had never seen a reaction in a patient with typhoid or typhus. I personally saw in Israel many cases of typhoid and typhus being treated with chloramphenicol. Nevertheless Dr. Harry Beckman states that on rare occasions he was compelled to stop treatment with CHLOROMYCETIN®. He has seen the drug become toxic to the hematopoietic systems and attributes this to the nitrobenzene ring in its chemical structure. Indeed he has reported a fatal case of aplastic anemia following prolonged use of chloramphenicol and is about to report 2 additional cases of a similar nature from one of the hospitals with which he is associated. Thus he urges that close study of the blood is necessary in all patients who are receiving chloramphenicol or chloromycetin for more than a short time.

Obviously some mechanism is needed, per-

haps established within the drug industry itself, to investigate extraordinary results when new drugs are used. Arrangements could be made to send records to a central registry to determine any multiplicity of cases, and investigators might go out to measure the hazards and conditions of use. The antibiotics are often used so carelessly that even the manufacturers warn constantly against such an unscientific approach. These drugs save lives but we ought to develop technics so lives will not be forfeited to reactions to the drug itself. Typhoid *in toto* is a far greater menace than the risk of chloramphenicol. Physicians in Israel feared blood dyscrasia far less than typhoid.

The pharmaceutical industry in the United States is one of the largest and most important industries in the world. It has conferred benefits to human life far beyond any other industry; it has postponed death by innumerable years for billions of people. It has given mankind freedom from fear and pain and suffering. It adds greatly to the world's goods in production of food and clothing directly and, in fact, of everything else indirectly. From the United States the products of our factories go out to extend health and life wherever they can be carried. Through the World Health Organization, the World Medical Association and the United Nations great benefits are being extended to every man.

Perhaps the first step in establishing a central agency to accumulate information as to the mechanisms involved when deaths occur associated with the use of new and complex drugs would be the convening of a committee to consider personnel, facilities and ways and means. This agency should have available every scientific aid and advice as well as the means of collecting information whenever toxic reactions to a drug are suspected. The cooperation of the pharmaceutical industry in establishing such an agency is vitally necessary to its success.

MORRIS FISHBEIN

THE NATIONAL CANCER INSTITUTE

THE National Cancer Institute of the Public Health Service has been making surveys of the incidence of cancer in major cities and has already published reports on Atlanta, New Orleans, San Francisco, Denver, Pittsburgh, Chicago, Dallas, Birmingham and Detroit. Now comes a report on Philadelphia with some striking observations. A comparison is made between 1948 and 1938 when a similar study was made.

In 1948, 18,282 cases of cancer were seen as compared with 13,185 in 1938. The incidence rate for 1948 is thus 341 per 100,000 compared with a rate for 1938 which is 26 per cent lower. The greatest increase noted was for cancer of the bronchus and lung for which the rate rose 101 per cent in the 10 year period. These apparent increases are believed by Dr. John R. Heller to be due to better reporting by physicians, improvement in diagnostic and case-finding methods and increase in the average age of the population.

In 1948, 85 per cent of all reported diagnoses were confirmed by the microscope compared with but 68 per cent in 1938. The percentage of microscopically confirmed diagnoses increased from 39 to 72 per cent for cancer of the stomach and from 44 to 68 per cent for cancer of the prostate. Again the significance of early diagnosis is emphasized by the fact that 81 per cent of patients diagnosed while the disease was still localized survived 12 months; of those not diagnosed until nearby tissues were involved, only 50 per cent survived 12 months, and of those not diagnosed until distant metastases appeared, only 27 per cent survived 12 months. Among men the most frequent sites were digestive system, respiratory system, genital organs and skin; among women, digestive system, genital organs and breasts.

The value of these important surveys cannot be overestimated.

MORRIS FISHBEIN

The Changing Medical Scene

CYRUS C. STURGIS*

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C. C. STURGIS

THE historian who looks back on the medical scene from about 1900 to the present will undoubtedly concede that it has been the most fruitful period in history. In fact, the medical progress in these years has been greater than during any other time in the entire history of the world. Think of the accomplishments—beginning with the introduction of diphtheria antitoxin at about the turn of the century and ending with the control of infection by the sulfonamides and antibiotic preparations which are probably the greatest of them all.

Furthermore it is not rash to predict that the accomplishments of the interval between 1950 and 2000, or the next 50 years, will even surpass those which have already been achieved. With all these advances it may be well to consider carefully, has this amazing progress created any special situations of importance? The answer is *yes*, it has been responsible for one of the largest problems ever presented to the medical profession.

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Presented before the thirty-seventh annual Assembly of the Interstate Postgraduate Medical Association at Cleveland.

The Greatest Problem of Them All!

The difficulty is this. How is the physician to familiarize himself with the current advances which are reported in the literature? To rely entirely on textbooks is not adequate. They are essential and have their place, which is to give the proper background of a subject. Progress is so rapid, however, that books must be obsolete in some respects before they reach the reader.

If a patient is under your care with a serious disease, how can you be certain that you are providing the best medical attention available? How horrible to consider that your patient may have succumbed or developed a serious but preventable complication just because you have not been familiar with some recent advance in medicine which would have averted it. Undoubtedly the most pressing problems in medicine today are (1) how to keep informed of the developments in medicine and (2) how to evaluate various new forms of diagnosis and treatment which are of practical importance.

The Quest for Knowledge

A great stimulus to continued learning is the quest, or one might almost say the passion, for knowledge. It may not be exactly the stimulus of seeking knowledge but actually a sensation of dissatisfaction or discomfort if one is conscious of the incompleteness of his information. This is especially true if it has

a bearing on some practical question which confronts him. It is difficult to analyze this uncomfortable state; perhaps it is concerned with conscience or devotion to duty. It is a valuable sensation to have and nurture and one to which we are indebted because it is an effective incentive which urges us to expand our knowledge.

A great many really industrious persons do not especially like work for its own sake. They enjoy only the things which work provides. In some instances it is money, affluence and comfort, but the true physician enjoys labor chiefly because he thereby develops a peace of mind which comes only from knowing that he has provided the best care for his patients.

Some idea of how difficult it is to keep informed of the advances in medicine is apparent when one considers the "Current List of Medical Literature" which is published monthly by the Armed Forces Medical Library. It contains listings of between 9000 and 10,000 medical articles each month, or over 100,000 per year, many of them in foreign languages. Even if one were able to read a goodly number of such publications, another problem of great importance arises. How can the information imparted by such articles be evaluated by the individual reader? In other words, how can the practitioner sift the good from the bad, the authentic and genuine from the speculative and spurious? And most important of all to the practitioner, how can this information be used in everyday practice?

How to Deal with the Problem

A number of procedures can be of service in dealing with this problem. One is to impress on the mind of the undergraduate medical student early in his career that medicine is constantly progressing at a rapid rate. Hence the habit of reading the current literature should be so thoroughly ingrained in him that he will be likely to follow such a practice continuously throughout the remainder of his professional life. We try to make it clear to the student that his training is only initiated during his undergraduate medical school days. Furthermore he should be acquainted with the idea that medicine is progressing so rapidly it is necessary to graduate him "on the run." We admit readily that even an entire faculty of a medical school cannot know all there is to know about medicine. If they did on any given day, parts of it would be obsolete by the following morning.

With these matters in mind, therefore, the great stress in medical school should be placed not on teaching students *what to think* but rather on *how to think and evaluate*. In order to keep the importance of the current literature before the medical student in the clinical years, we at the University of Michigan are now in the process of preparing a representative list of authentic and useful recent articles from the current literature dealing with the various divisions of internal medicine. A similar procedure has been used at other medical schools in recent years with success. Such a list, when revised at frequent intervals, serves two purposes in addition to providing factual knowledge: (1) It emphasizes the importance of the current literature, and (2) it indicates that discretion and judgment are essential in selecting articles which are to be read. We hope that this selected bibliography will provide at least the foundation for good reading habits after graduation from medical school.

Reading to the Point

What can the individual physician do to keep informed concerning the important rapid advances in medicine? Admittedly it is an added burden and a struggle for the average overworked, tired physician. It must be done, however, or one will fall far behind the times in a remarkably short time. The following suggestions are offered for your consideration.

Certainly one should not read aimlessly in medicine. Often it is a waste of time. The golden opportunity is when one attempts to expand his knowledge by consulting the literature apropos of a clinical problem with which he is confronted at the moment. For example it *might* be of interest to the medical student or intern or practitioner to read about the modern treatment of subacute bacterial endocarditis just as a matter of general knowledge. But consider how stimulating, practical and

useful this information would be at a time when he was confronted with a patient who had this disease and whose life depended on the treatment which was to be administered. The presence of a patient who illustrates a point, who raises the question of the correct diagnosis, treatment and prognosis, always vitalizes our quest for knowledge and imprints it more firmly on our minds. It then becomes a part of us, and forms a basis for accumulation of knowledge which we term "clinical experience."

Systematic Reading

Let me emphasize a second aspect of efficient reading. Make every effort to have at least a small library available. The pooling of interest of all the physicians and use of the city, county or hospital library as a place to locate the accumulated literature, with a community effort, should provide a sufficient number of current publications to supply the need.

The development of local hospital staff exercises are essential for the development of our knowledge. They necessitate the perusal, evaluation and concentration of medical literature for presentation at staff meetings, journal clubs, x-ray medical conferences and clinicopathologic conferences. In my own department I have the following meetings during the week, each one of an hour's duration: Journal Club; Fatal and Operative Case Conference; Medical X-ray Conference; Medical Staff Meeting, and periodically but not every week, clinicopathologic conferences before the entire senior class of medical students. If one would attend such meetings regularly he would absorb each time a sufficient amount of new material to make it worth while.

In addition the physician should attend regularly his county and state society meetings, and make an effort once or twice a year to participate in such annual sessions as this one. This organization to me is a model of its kind; the programs are made up of carefully selected topics, the speakers are experienced, and the presentations are of the proper length. Furthermore the organization has had such an extensive experience over many years that it can present the maximum amount of information in a relatively brief time. *If a physician could attend only one postgraduate course a year, in my opinion this should be the one.*

The Hospital as a Postgraduate Teaching Center

In recent years the Department of Medicine of the University of Michigan has sponsored a Thursday afternoon weekly postgraduate session especially for physicians of the local community. Those who have attended the course are of the opinion that it might well be used as a pattern by other hospitals. The plan is as follows: Each Thursday afternoon at 1:30, two 75 minute informal clinics are given on medical topics which we believe are of interest to the practitioner. The clinics are begun by the presentation of 1 or 2 patients who illustrate the points to be emphasized. These exercises are attended by 50 to 60 physicians, most of whom are in general practice in the immediate community, although some drive each week from distances as far away as 90 miles. At 4:00 P.M., after two and one-half hours of such discussions, those in attendance are invited to our medical staff conference which lasts an hour. The total clinical instruction, therefore, is for a period of three and one-half hours a week, over an interval of eight months each year.

A staff member gives such a clinic of one and one-fourth hours about every two months and hence the added teaching demand is not great on any member of the department. The topics are selected on the basis of their practical basis of usefulness to those attending. Samples of the clinics which have been given recently are: "The choice of treatment of disorders of the thyroid gland"; "Therapy of infections with antibiotics and sulfonamide drugs"; "The diagnosis and treatment of hematologic disorders"; "The management of patients with diabetes," and "The early diagnosis and treatment of pulmonary tuberculosis."

Specialization

It has been claimed by some that specialization is the *only* answer to keeping abreast

with the appalling amount of new information in the many fields of medicine. This solution has its dangers when one limits his knowledge strictly to a single narrow aspect of medicine. It is restricting and dangerous. I do not believe that a physician can take care of "parts" of a patient. On the other hand it is my opinion that there is proper place for what I call "limited specialization." I am now speaking especially of internal medicine but the same trend of thought might well be applied to all fields of medicine and surgery. The plan I find satisfactory is this: I insist, first of all, that the physician be an internist with a broad interest in the entire field of medicine. As such he is available for consultation with other members of the department when it is thought that he may have additional and specialized information which will be useful in the care of any given patient. Such a man is usually doing some type of investigative work in the field of his special interests. Furthermore he undoubtedly has a better knowledge of the literature of this branch and should be able to evaluate it more satisfactorily.

I should think that this form of limited specialization might be useful in even a small community. One practitioner might develop a special interest in cardiology, for example, and another in hematology or some other specialty. In each instance, however, they should not limit their practice to such specialties but accept patients with all types of disease states.

What Are We Doing That's Wrong?

In my almost 40 years' association with the medical profession I have come to develop a great admiration and respect for it and its members. I am exceedingly proud of the fact that I am a doctor and that my colleagues, in general, are the types with whom I desire to be associated. With exceedingly rare exceptions, they are scrupulously honest, hardworking, self sacrificing and imbued with the idea of helping others.

It is easy to agree on the favorable things about an organization or profession. We are more reluctant to discuss some of the things which are less favorable. For our own good, however, these too should be brought to light and discussed frankly. In other words, everyone might profit greatly by asking periodically, *what are we doing that's wrong?* My remarks are directed toward the younger men, first, because I have a special interest in them on account of my association with many who are in training; second, because they are more easily corrected, and depend on us for guidance; and third, because they are one of our most valuable assets and it is so worth while to help them.

Failure to Appreciate the Value of Hard Work

I have noted a trend, which certainly has not reached flagrant proportions, characterized by a failure of interns and residents to appreciate the importance of what is one of the most fundamental principles for success in medicine. *This basis of success is persistently purposeful, hard work.* It is unnecessary for me to tell you that the life of a successful physician is characterized by long hours, tense and sometimes irritating situations, and inability to control one's time. Most of us know also that success in our profession is related chiefly to two things, namely (1) intelligence which varies from average to sheer genius and (2) the ability to carry on persistent work.

There are few geniuses in the world, probably less than a dozen per generation in medicine, or perhaps even not that many. Even Osler says that he was endowed with only "mediocre brains" and yet he was the outstanding physician of the generation in which he lived. *But we can all work!* Perhaps some insight into the reason for his success may be obtained from the following sentence which Osler also said, "The master word in medicine is work . . . Though a little one, it looms large in meaning. It is the open sesame to every portal, the great equalizer in the world, the true philosopher's stone which transmutes all of the base metal of humanity into gold." The thought expressed by Charles Kingsley has always appealed to me and would be a good thing for every person in the world to have hanging over his bed to be read every morning, as an inspiration for

each day. It is as follows: "Thank God that every morning when you get up that you have something to do which must be done, whether you like it or not. *Being forced to work, and forced to do your best, will breed in you temperance, self-control, diligence, strength of will, content, and a hundred other virtues which the idle will never know.*"

Not long ago an occasion arose which made it necessary to evaluate a resident's services. We were to determine whether or not he should be recommended for a position in another hospital. We were undecided but came to the conclusion that he lacked something which we could not define precisely. Finally one of the older members of the department, known for his industry and accomplishments despite his handicap of pulmonary tuberculosis, said, "The trouble with that man is that he does not work until it hurts." This, I think, might serve as a motto for us all.

The modern intern or resident, at the present time, although he will always take care of emergencies, demands much more "free time" than those of 25 or 30 years ago. He asks that he be completely relieved of his duties on every other night and every other week end, and frequently considers that his day is finished promptly when the five o'clock whistle blows. What is the cause of this? One important factor is that many interns and residents and even undergraduates are married, which in part at least is attributable to the delay in professional education occasioned by the war. Marriage, however, has many compensations and I see no reason why it should be frowned upon in young medical men. It may be a good opportunity at the very beginning of the union, however, to indoctrinate the young wife with what is to be expected in the future when her husband enters the busy and demanding practice of medicine.

The most baneful influence, however, is not the marital state but the *five day week* which is insidiously working its way into the life of every man, woman and child of this country. For several years in many hospitals there has been a five day week enforced for all technical workers, and more recently this has been applied in the nursing profession. I have no definitive arguments to offer against the five day week in industry, and possibly in the nursing profession, but I should like to call attention to three possible harmful effects which must be evaluated and weighed against the benefits thought to be derived from such a plan: (1) The imposition of a five day week, of course, necessitates the use of more nurses and necessarily increases the cost of medical care, which is to be deplored. Sometimes, moreover, it is not possible to provide additional nurses due to the universal scarcity of personnel; (2) it is not always possible to obtain essential routine laboratory studies including x-rays over the week end because of the five day week for laboratory workers; this often prolongs a patient's stay in the hospital. These two objections are real and should be corrected if possible; (3) the greatest objection, in my opinion, of the 40 hour week in the medical profession is the "bad example" which it provides for the younger medical men. The young intern wants to know why he should be denied the 40 hour week if the nurses and other hospital employees have it. I understand his attitude, and am sympathetic to a certain extent. Moreover, we could manage to operate the hospital even if such an innovation were to apply to both interns and residents. That is not the most important point. *The real issue is that they are deprived so often of a golden opportunity to learn*—an opportunity which presents itself only in the earliest hospital training years and which when curtailed will never return again. Such experience is precious and when lost is irretrievable. There may be good reasons for a five day week industrially, but for an institution devoted to the care of the sick such a program is a definite handicap to the care of the patient and the learning of the resident staff.

The Decline of the Art

Although we are overwhelmed with scientific discoveries, medicine has not continued to advance from every standpoint. It is disappointing to observe the tendency toward what has been called the decline of the art. There is a regrettable inclination, especially

on the part of the younger physicians, to treat the disease rather than the patient. Science with its miracles cannot always make a patient happy, although it may completely eliminate the organic disease which is present.

We all acknowledge with pride the accomplishments of science, but many patients need more than strict scientific care to rehabilitate them. The hazards of science are well expressed by Henry Luce who said aptly, "Science, in these years, gentlemen, has indeed marched on—not only your physics and chemistry but also your economics and sociology and psychiatry . . . Science has marched on to chaos . . . And now if science will kindly get out of the driver's seat and under the hood where it belongs, Man will take over—Man, as Man."

In other words, a physician, and in fact anybody else, particularly those who guide the world, need such unscientific things as personal integrity, common sense and judgment in human affairs, interest, understanding, compassion, patience and humility. These sterling attributes in a physician go to make up his attitude and demeanor toward the general management of the patient which we call the art.

I am inclined to agree with the classic statement of Sir Andrew MacPhail (1933) in regard to one difficulty which we have in teaching modern medicine: "I am well aware that in these days, when a student must be converted into a physiologist, a physicist, a chemist, a biologist, a pharmacologist and an electrician, *there is no time to make a physician of him.* The consummation can only come after he has gone out into the world of sickness and suffering, unless indeed he is so bemused, his instincts so dulled, his sympathy so blunted by the long process of education in those sciences, that he is forever excluded from the art of medicine which was to Hippocrates 'the art of all art.' Armand Trousseau the great French clinician said something to be remembered when he pounded vigorously on the table and shouted to a group of physicians, '*A little less of the science and a little more art, gentlemen.*' "

Do not mistake my criticism. Science has saved millions of lives and the art can rarely be credited with preventing death unless it spares one from self destruction. I would modify Trousseau's statement to read "just as much science and more of the art." We have all known of physicians who fail because they depend largely on the art and adhere to the old symptomatic form of therapy while a completely curative, scientifically developed treatment is disregarded. This may be superficially attractive to the patient for a while, but the results are sometimes tragic as there may be a high mortality and morbidity. The ideal aim, of course, is the proper combination of the art and the science.

These days, as a teacher of medicine, I am not concerned about the scientific knowledge of medicine which our students possess when they graduate from medical school. This with the training they receive in the intern and resident years gives them a scientific background superior to that acquired in previous generations. In other words, the teaching of the scientific aspects of medicine, I believe, is accomplished better now than ever before in the history of the world. Yet the public has some righteous cause for complaints which are often attributable to a failure on the part of the physician to practice the art. It is a difficult subject to teach. A knowledge of it is impossible to acquire by reading a book. It must be practiced, encouraged, stimulated, guided and fostered by those of us who as preceptors come in daily contact with the younger members of the profession.

The Paucity of Time

A criticism one hears frequently from patients these days is that their physician does not spend a sufficient amount of time in discussing their complaints or making clear to them the basis of their projected treatment and the outlook for recovery. You can be sure that this situation, if true, is one which will not be remedied by the imposition of socialized medicine. Even the most rabid advocate of this form of socialism claims no improvement in this aspect of practice.

The obvious curtailment of time in discussing a patient's condition with him, or his rela-

tives, can be interpreted only as an indication that the physician has more important things to do. In other words the patient feels slighted, hurt and dissatisfied. He frequently is greatly pleased by the attention given him by a fourth year student on the wards of a teaching hospital. This is for one reason mainly. He does take the time and trouble to listen at great length to his complaints.

The art takes time. There is no shortcut. The physician's time is limited. One of the main problems of the modern physician, then, is how to use his time to the best advantage with the patient without slighting either the science or the art of medicine. Someone said, The difficulty in the satisfactory solution of a perplexing question is to delineate it clearly. There is nothing obscure about this situation. The solution is in the hands of each individual physician. Will you or will you not practice the art along with the science?

Now let me close with a brief reference to another aspect of a physician's life. We are all citizens with a great stake in this country's present and future. In these troubled times, in our darker moments one sometimes wonders what the future holds. All of us know, however, that we can really regard what is to come with optimism. It is desirable for all of us to have some concept which may guide us in thinking about the social, political, industrial and financial future of the world. We all need a code bearing on these. Here is mine, offered for your consideration.

"You cannot bring about prosperity by discouraging thrift. You cannot strengthen the weak by weakening the strong. You cannot help the wage earner by pulling down the wage payer. You cannot further the brotherhood of man by encouraging class hatred. You cannot help the poor by destroying the rich. You cannot establish sound security on borrowed money. You cannot keep out of trouble by spending more than you earn. You cannot build character and courage by taking away man's initiative and independence. You cannot help men permanently by doing for them what they could and should do for themselves."

I wish I could say that I had written those words of wisdom but I did not. A man far wiser than I, one of our greatest Americans, Abraham Lincoln, was responsible for the statement of those fine principles years ago.

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1. Reich, W. J., et al. (1952), A Recent Advance in Estrogen Therapy. II. American J. Obst. & Gynec., 64:174, July.

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Letters from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

LONDON

Christmas disease—A new blood disease, a variety of hemophilia, was described recently by a group of physicians and laboratory workers at Oxford (Biggs, et al., *British Medical Journal*, December 27, 1952, p. 1378) under the name "Christmas disease." The disease was named after 5 year old Stephen Christmas, the first patient examined in detail. The naming of clinical disorders after patients was introduced by the Victorian surgeon Sir Jonathan Hutchinson and is familiar from serologic research; it has the advantage that no hypothetic implication is attached to such a name. But already protests have been made by doctors that the name should be changed to one less closely associated with the season of happiness and good will, and the International Hemophilia Society is also protesting the name.

Seven cases were recorded in which the usual clinical and laboratory features of hemophilia were present, but blood thromboplastin formation was grossly reduced because of the deficiency in the blood of a factor called the Christmas factor; and in the treatment of hemorrhage in cases of this disease concentrated preparations of antihemophilic globulin were ineffective. The same disease appears to have been described in America, though not as a separate entity, by Dr. Aggeler and others in the *Proceedings of the Society for Experimental Biology and Medicine* (New York) in 1952, and also by Drs. Schulman and Smith, in *Blood*, in the same year.

Butazolidin in arthritis—Claims recently have been made for the value of BUTAZOLIDIN® (B.T.Z.) in treating a wide variety of painful skeletal conditions, particularly ankylosing spondylitis, degenerative joint disease of the spine, and Paget's disease of bone, and that in rheumatic fever the drug is at least as effective as salicylates. The drug is not given to patients with a definite history of peptic ulceration, and is given cautiously to those who have marked dyspeptic symptoms.

It was the chance use of butazolidin as a solvent of aminopyrine that led to claims of its potency as an effective analgesic and antipyretic drug. A series of cases now exceeding 200 has recently been reported and the degree of relief experienced was undoubtedly impressive. It is to be observed that the drug is analgesic and antipyretic rather than curative in its effects, and it must be given with caution, for at least 1 death has occurred when a patient was under treatment with it.

College of General Practitioners—To the numerous medical organizations and associations already existing in England has just been added another called the College of General Practitioners. This has been founded mainly as a protest against the lowering of the status of general practitioners in Britain since the introduction of the National Health Service, and to try to avoid the danger of the family doctor becoming "a mere medical shopwalker indicating the appropriate department."

Following correspondence in the medical journals, a "Steering Committee" was set up in 1952 with Mr. Henry Willink, Master of Magdalene College, Cambridge, and a former Minister of Health, as chairman, and such well known "planners" as Sir Wilson Jameson, late of the Ministry of Health, and Professor Mackintosh, Professor of Public Health of London University, along with the editor of *The Practitioner*, a professor of surgery, and a number of well known general practitioners, including Dr. G. F. Abercrombie of London, who has been nominated as the first chairman of the council of the newly founded college.

(Continued on page A-24)

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It may be suggested that the foundation of this college is really a criticism in itself of the rather feeble leadership that the British Medical Association has had since the war. If the B. M. A. had shown a little more backbone, stood up to the political parties of all shades of opinion, and had not allowed the Royal Colleges of Physicians and of Surgeons to become politically minded as well as academic, there would have been little need for this new college. Nevertheless, the report of the "Steering Committee" was unanimous that such a college should be founded, and if it will manage to escape becoming yet another diploma factory and to keep completely out of politics, medical and otherwise, perhaps it may prove more valuable than appears likely at the moment.

AMSTERDAM

Tuberculosis data— Over a year ago voluntary examinations for tuberculosis were started by means of x-rays of the thorax and the tuberculin test. By November 27, 1952, 200,000 Amsterdam residents had been examined. 82 per cent of them recommended for examination. Of these, 230 showed active tuberculosis and 400 dubiously active tuberculosis.

Everyone in the province of Zeeland was checked, the examinations taking place from October 1950 to September 1952. Approximately 19,000 of the 270,000 inhabitants refused examination; 260 cases of active pulmonary tuberculosis and 31 cases of surgical tuberculosis were reported. Meanwhile a second series was started in Zeeland immediately after the first examination and approximately 60 new cases of tuberculosis were found.

Although the yearly morbidity rate has gradually decreased, it is still approximately 30 per cent higher than in 1939. In 1951 approximately 15,000 new patients were registered with the consultation offices for tuberculosis as compared with 16,108 in 1950. In an average population of 100,000, this means a decrease from 159.4 to 146. The yearly cost of tuberculosis care, due to

the high morbidity, amounts to approximately 50 million guilders.

Since the war the mortality rate of this disease has, however, decreased beyond expectation and is considerably less than it was before the war. Evidently modern methods of treatment with new drugs and surgery play important roles. In 1951, 10 persons per 100,000 died of tuberculosis in the Netherlands, whereas in 1945 this figure was 86.

Tuberculous reinfections—Opinions vary concerning the development of tuberculous reinfections of the lungs. The definition of a reinfection is a tuberculous inflammation of the lungs that develops after the primary effect has long since healed. Some believe that reinfections develop exogenously as a result of a new infection with tubercle bacilli; others believe that they develop endogenously through tubercle bacilli originating from the primary complex.

An interesting paper from Dr. Th. G. van Rijssel (Nederl. tijdschr. v. geneesk. 96:3176, 1952) appeared on this subject. In Groningen, in the years 1948, 1949 and 1950, he and his co-workers carried out 261 autopsies of patients who had not been admitted to the hospital because of tuberculosis. Systematically, tuberculous processes or sequelae were looked for in the lungs and in lymph nodes of neck, chest and mesentery.

In 1933 Dr. M. Straub carried out a similar investigation in Amsterdam. Of the persons between 20 and 40 years old examined, 87 per cent appeared at that time to be infected and in the older persons the percentage was still higher. In Groningen the percentage is much lower: 45 per cent in the age groups from 20 to 40 years and in older people approximately 65 per cent. Straub found that 50 per cent of affected persons from 20 to 40 years old showed reinfection and that reinfection occurred in 70 per cent of persons over 40 years of age. Van Rijssel's results indicated that only 1 out of 5 cases in every age group showed evidence of reinfection. These figures are so much lower than the findings of Straub that it is highly improbable that the pathogenesis can be explained by an endogenous reinfection. "Why," van Rijssel asks, "should the inhabitants in the Amsterdam district be three times more susceptible to endogenous reinfection than the inhabitants of Groningen?" Moreover, van Rijssel points out by means of statistical data that in Amsterdam, before 1935,

(Continued on page A-26)

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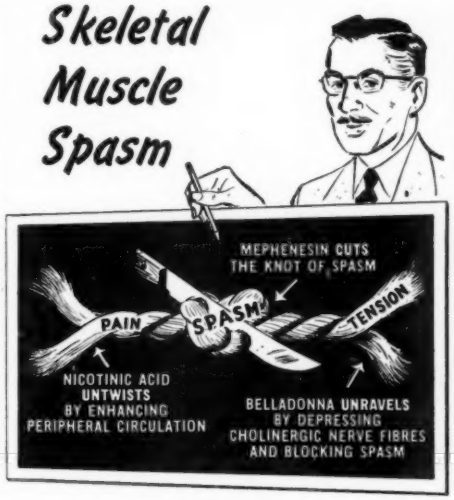
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infection occurred much quicker than now, 15 years later, in Groningen. In Amsterdam, for instance, a 50 per cent infection rate was already reached at the age of 15 years, while in Groningen this percentage was reached only after 30 years of age. In Amsterdam, therefore, the chance of exogenous reinfections must have been much greater in 1933, and so van Rijssel concludes that following the development of a primary complex a new infection with tubercle bacilli may again cause a tuberculous inflammation—an exogenous reinfection.

Investigation in Dutch New Guinea—Dr. S. Kooyman, conservator (assistant professor) at Leyden University, has started an investigation of the population of New Guinea. He is being assisted by two Dutch physicians from South New Guinea (Merauke), Dr. Goorhuis and Dr. Veeger.

This survey is intended to serve as a pattern for similar investigations in other parts of the Pacific. They are organized by the South Pacific Commission and especially concern the reasons for the depopulation, which occurs in different parts of the Pacific. There are various theories on this subject: it is certain that in the different races in this territory more boys are born than girls and it is possible that through contact with Western civilization more infectious diseases have been brought into the country, resulting in a decline of the population.

The southern part of New Guinea has been chosen for this experiment. It is possible to base these investigations partly on data systematically collected during the past 50 years by missionaries working in that territory.

Future development of the Netherlands population—The Centraal Bureau voor Statistiek (Central Office for Statistics) has published a study on the future development of the population of the Netherlands (De Haan, Utrecht).

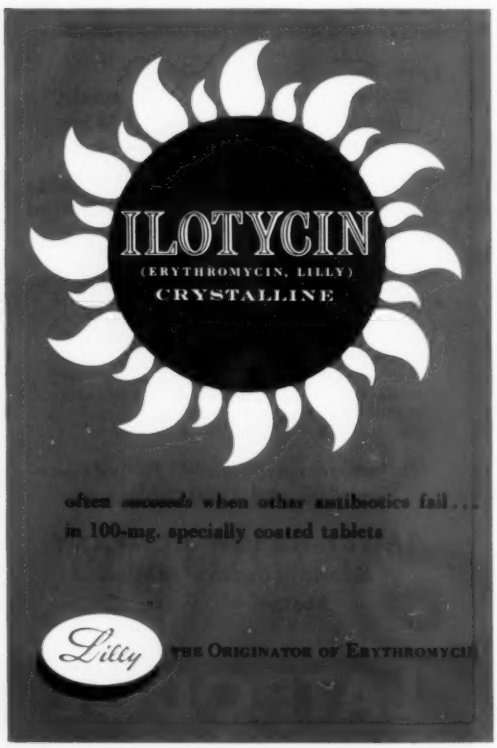
It is obvious that a large part of this study must be assumed. Nevertheless the factors determining the development of the population have been considered as much as possible—for instance, emigration based on those who left in 1950. The conclusion was drawn that in 1980 the number of children who will have reached the age for compulsory education will be decreased by approximately 300,000 (total, 1,300,000).

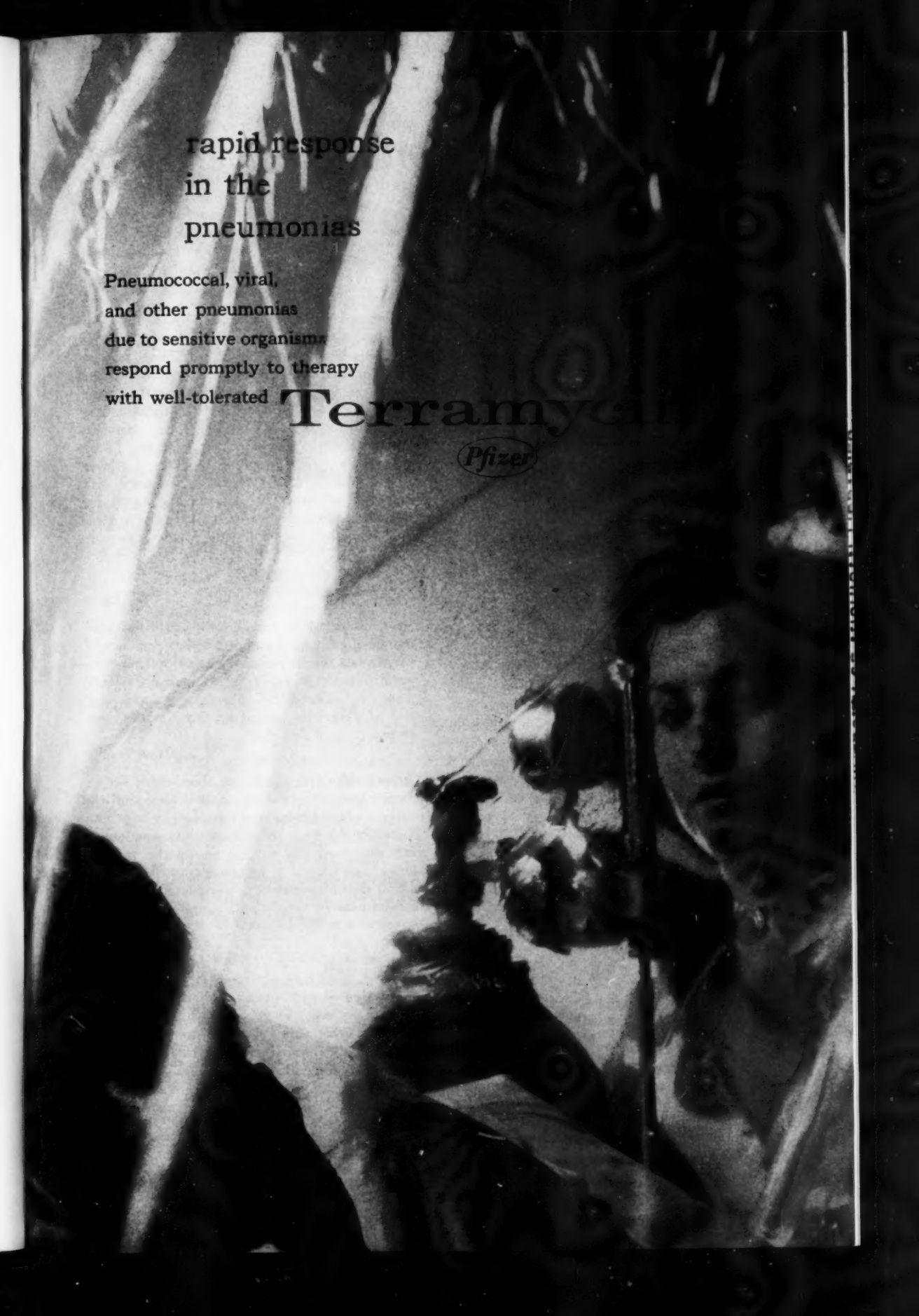
The following figures are calculated:

	1949	*1959*	*1969*	*1979*
Birth rate per 1000	23.7	17.9	17.2	17.0
Mortality rate per 1000	8.6	8.7	8.7	10.5
Population on December 31 (thousands)	10,027	11,198	12,134	13,036
Percentage over 65 years of age on December 31	7.7	8.8	10.1	11.1

In addition to these figures, many others are mentioned (expected number of marriages, average size of family, etc.).

Infectious hepatitis and physicians—In a communication to the editors of *Nederlandsch tijdschrift voor geneeskunde*, published in a recent issue, Dr. I. Boerema, professor of surgery at the University of Amsterdam, observed that infectious hepatitis frequently affects physicians and particularly surgeons, not only in the Netherlands but also elsewhere. He thinks it not unlikely that infection may be caused through injury during an operative procedure. The chance of infection may well be increased if blood or plasma is given to a patient during the operation. In order to investigate the problem further, he has requested every physician in the Netherlands who has suffered from infectious hepatitis to report this to him.

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Your Questions answered

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• VITAMINS FOR ACNE

Question: What is the theoretical basis behind the prescribing of large doses of vitamin A for acne? One of my patients has been taking 200,000 units daily for some months. Is there any danger to continuing this treatment?

M.D.—Idaho

ANSWER: The theoretical basis for prescribing large doses of vitamin A in acne vulgaris is premised on the fact that in certain cases of acne there exists hyperkeratinization of the follicle, resulting in follicular plugging similar to that observed in hypovitaminosis A. Although there are many reports of hypervitaminosis A in infants and children, I am aware of only one report of chronic vitamin A poisoning in an adult (Sulzberger, Marion B. and Lazar, M. Paul: Hypervitaminosis A: Report of case in adult. J.A.M.A. 146:788-793 [June 30] 1951). There are many reports of acute vitamin A poisoning in adults after ingestion of polar bear livers, which often contain as much as 15,000 to 18,000 U/G of vitamin A. I have seen many adolescents ingest 200,000 units of vitamin A daily for many months with no evidence of vitamin A poisoning and also without any apparent benefit to the acne.

BEDFORD SHELMIRE

• DRUGS IN TREATMENT OF HEPATITIS

Question: Are any drugs of value in the treatment of a clinically mild case of hepatitis occurring during the course of infectious mononucleosis? In such a case which sedatives or narcotics may be prescribed in the usual therapeutic dosage without hazard?

M.D.—Connecticut

ANSWER: No drugs of any known value are available for the treatment of hepatitis occurring during the course of infectious mononucleosis. From the standpoint of dietary treatment and recommendation for physical rest, the same principles as are applicable to the treatment of viral hepatitis would apply. It is probable that sedatives or narcotics could be prescribed in the usual therapeutic dosage without hazard in the particular case described. It is thought that, as a general rule, sedatives and narcotics should be used with caution in any patient who has diffuse liver injury (viral or toxic hepatitis; cirrhosis of any cause). It is probably wise to use such drugs, if necessary, in one-half the customary dose until the patient's tolerance for the particular medication is determined by experience.

F. W. HOFFBAUER

• VAGINISMUS DURING PREGNANCY

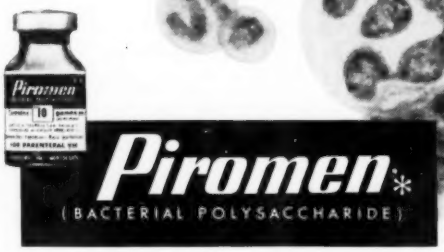
Question: A 24 year old primipara in the third month of pregnancy shows a rather pronounced vaginismus which makes a vaginal examination unsatisfactory. What is the recommended treatment of this condition in pregnancy, and what sort of difficulties caused by this condition can be expected on delivery?

M.D.—New York

ANSWER: Monilial infestation occasionally occurs during pregnancy and produces itching and tenderness of the vagina and introitus. In each case there should be a microscopic examination of any discharge which accompanies the vaginismus. I don't know of any sure cure of this condition during pregnancy. Various suppositories can be used by the patient. Usually they consist of gentian violet in some form. Care must be taken by the patient that the suppository is not inserted into the os cervix. The area can be cleansed by the physician or his nurse by an application of aqueous or aqueous-acid solution (1 or 2 per cent) of gentian violet. This causes a deep purple stain on the skin and on the clothes, and care must be taken to avoid this.

No harm should arise from vaginismus which, usually, is on a neurogenic basis. It should not be harmful during pregnancy or labor and is

(Continued on page A-36)



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usually relieved by the vaginal dilatation accompanying parturition.

ROBERT D. MUSSEY

• SURGERY FOR POLYCYSTIC KIDNEYS

Question: Please advise if any surgery has been done on polycystic kidneys and, if so, what results have been obtained.

M.D.—Maryland

ANSWER: Palliative surgery on polycystic kidneys has been done in a few instances. The first reason for operating is to relieve pain produced by the pressure of the enlarging cysts on other organs or structures.

Some surgeons have attempted to improve the blood supply of the kidney by sewing this kidney to other structures, such as the omentum. A few surgeons have exposed the kidney to a flank wound so that repeated punctures of the cysts may be accomplished.

A few instances have been reported where a polycystic kidney has been removed when clinical and urologic evidence suggested that the contralateral kidney was slightly, if at all, involved in this condition which is practically always a bilateral change.

In addition to the relief of pain that is obtained when large cysts are punctured, some surgeons have reported that the blood chemistry is somewhat improved.

The length of the patient's life depends on the amount of functioning kidney tissue that he has. If any of this is taken away from him, it will shorten his life. Rarely do we find patients suffering from this disease who live to be 50 years of age.

GILBERT J. THOMAS

• TREATMENT OF NEURODERMATITIS

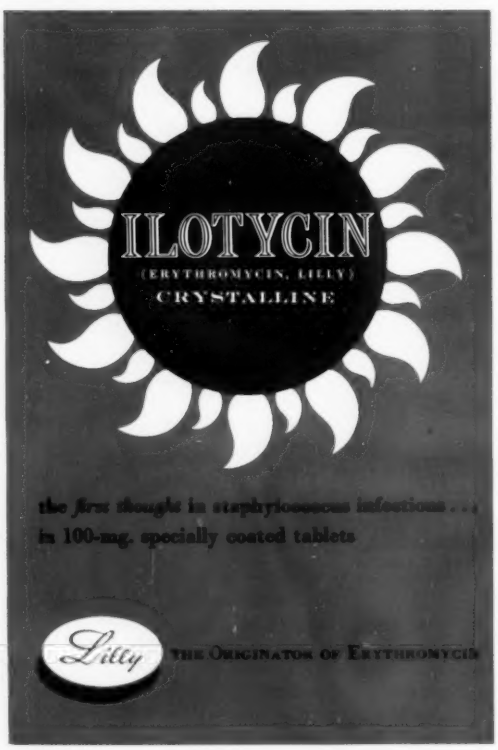
Question: A 27 year old single girl has had neurodermatitis since early childhood. At the present time the skin lesions are visible at both sides of the neck, the inner surface of the right upper arm and around the right knee. They are very itchy and although coal tar ointment seems to relieve the itch somewhat, she does not care to use it often because her skin turns dark after application of the ointment. X-ray and ultraviolet light treatments have been used without much benefit; this therapy also bothers her skin which darkens and wrinkles a great deal. Her mother has had the same condition for many

What are the modern treatments of neurodermatitis? In this particular case of long standing, what is the recommended and beneficial therapy? What is the latest concept about using cortisone or other hormone therapy for neurodermatitis?

M.D.—Montreal

ANSWER: The treatment of neurodermatitis consists of the local application of antipruritic lotions and ointments containing some form of tar, and the judicious use of fractional x-ray by a qualified dermatologist. When the above regimen fails, a complete change of environment, as a visit to one of the desert cities, often results in a complete remission of the eruption. Cortisone and ACTH are of only temporary benefit in this condition, the neurodermatitis usually recurring when these hormones are withdrawn.

BEDFORD SHELMIRE



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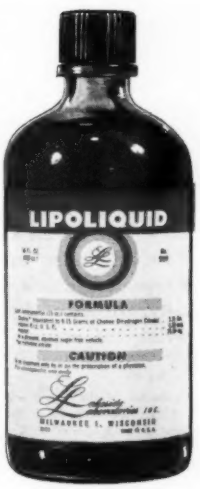

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CONGENITAL ANOMALIES OF THE HEART AND GREAT VESSELS*

THE author of "Congenital Anomalies of the Heart and Great Vessels" has also written a book on another phase of the subject, "The Electrocardiogram in Congenital Cardiac Disease," published in 1940. The present book is intended "to bring to the practicing physician the modern concepts of congenital cardiac disease in rather complete form, incorporating in particular the new material on this subject." In most respects this purpose has been achieved. The description of the individual anomalies is detailed and clear; some of the newer material is well integrated into the text, and the over-all coverage of the text is quite complete. A well arranged index is appended.

Unfortunately, the author has made use of illustrations to only a very limited extent. The subject is one which not only lends itself to, but also requires, pictorial presentation to help the reader, especially one who is not too conversant with the subject to begin with. The value of this book would have been immeasurably enhanced if the author had reproduced roentgenograms, electrocardiograms and other material pertaining to the subject matter, admittedly described with great clarity in the text. There is, for example, a lengthy description of clubbed digits and there is a detailed account of the collateral circulation in coarctation of the aorta; illustrations with appropriate legends would have made the reading simpler and more comprehensible.

Attention should be drawn to a number of inaccuracies which exist in the literature and which are repeated in this book. The subject of idiopathic hypertrophy of the heart is oversimplified, leaving the impression that it is an entity which can be easily recognized clinically. An enlarged heart in an infant, considered clinically to belong to the idiopathic group, has repeatedly proved to be one of several well recognized congenital anomalies but one in which the usual diagnostic features were not demonstrable during life. Unless this fact is constantly kept in mind, an opportunity to make the correct diagnosis by more detailed investigation will be lost. It is true that the correct diagnosis may prove of academic interest only, but infants with coarctation of the aorta or patent ductus arteriosus in congestive heart failure may present just such a picture. Infants with ventricular septal defects may die early because the pulmonary circulation cannot adjust to the large shunt of blood into it—the infant dies of heart failure when the main clinical finding is a markedly enlarged heart; similarly, anomalous origin of the left coronary artery from the pulmonary trunk and the dilated type of endocardial sclerosis can result in enlargement of the heart that is frequently labeled idiopathic hypertrophy.

An illustration of double aortic arch (which is borrowed from the literature) shows an innominate artery arising from an intact right aortic arch; this is developmentally incompatible, and careful examination of anatomic specimens of this anomaly will show that the homolateral common carotid and subclavian arteries arise independently from the arch.

The classification of coarctation of the arch of the aorta into the adult and infantile types is conventional. However, these terms have come to contribute less meaning as more is learned about this subject. It seems more appropriate in classifying coarctation to indicate, first, the relative positions of the coarctation with respect to

(Continued on page A-52)

*Congenital Anomalies of the Heart and Great Vessels. By Maurice A. Schnitker, M.D., Director of Medicine, St. Vincent's Hospital, Toledo. 306 pages with 19 figures. 1952, Oxford University Press, New York. $8.00.

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ductus arteriosus, whether proximal or distal to the ductus, and second, to indicate whether the ductus arteriosus is patent or obliterated. A coarctation lying proximal to the ductus has the same structural deformity as one which lies distal to it. The author further implies that those patients with coarctation proximal to the ductus arteriosus (referred to as the infantile type) do not survive because of additional malformations. This teaching should be put aside in view of more recent studies which indicate that early death in coarctation proximal to the ductus arteriosus is more often the result of left ventricular failure secondary to a combination of closure of the ductus and to inadequate collaterals bypassing the coarctation. The statement that microscopic examination of the site of coarctation shows deficiency of elastic and muscular tissue and an increase of fibrous tissue is incorrect. The structural deformity has been shown to be an abnormal infolding of the media accentuated by intimal thickening in this region.

The expression "hypoplasia of the aorta and of the aortic knob" is misleading and inaccurate as applied to the roentgenologic appearance of the aortic arch in atrial septal defects. Anatomically the aortic arch is normal in atrial septal defect. The roentgenologic feature referred to is explained by the fact that the aortic arch is merely rotated out of sight when viewed in the anteroposterior position in conditions such as atrial septal defect and in other conditions associated with right ventricular hypertrophy.

Certain other minor errors deserve comment. It is stated that a patent ductus arises from the pulmonary trunk; actually it arises from the left pulmonary artery. A patent ductus is stated to be common in pulmonary stenosis with intact ventricular septum. Such a finding has not been the common experience.

Under defects of the aortic septum the author includes the classic examples of persistent truncus, defect of aorticopulmonary septum, and aneurysm of the sinus of Valsalva. All of these in turn are listed under the cyanotic group of congenital heart diseases. While the classic examples of persistent truncus arteriosus belong under this category, the other two conditions do not. Aorticopulmonary septal defect would better have been placed in association with patent ductus arteriosus under the cyanosis tardive group even though it is agreed that a defect in the aorticopulmonary septum represents a minor form of persistent truncus arteriosus. Aneurysm of the sinus of Valsalva, however, is not universally accepted as resulting from a malformation in the septum which partitions the embryonic ductus arteriosus into aorta and pulmonary trunk. In any event patients with aneurysm of the sinus of Valsalva in the unruptured state are acyanotic; those in whom the sinus ruptures, so that the aorta communicates with either the right atrium or right ventricle, belong to the cyanosis tardive group.

The sections on treatment are discussed in considerable detail. Most experts will, however, consider the author's criteria for the selection of patients with patent ductus arteriosus for surgical closure too conservative. The sections on the clinical phases of congenital anomalies deserve the major credit.

As a convenient reference handbook, therefore, this publication should prove of value to the practicing physician.

T. J. D.

► PROGRESS IN FUNDAMENTAL MEDICINE

Edited by J. F. A. McManus, University of Virginia. Contributors: Paul Cannon, J. A. Cunningham, Paul Klemperer, Albert Kligman, G. K. Mallory, Tracy B. Mallory, J. C. Paterson, L. B. Stoddard, W. Kenneth Cuyler and J. P. Wyatt. 316 pages with 74 illustrations and 2 color plates. 1952, Lea & Febiger, Philadelphia. $9.00.

Gathered together in this book are discussions of several varied topics which have in common current clinical and pathologic importance. Perhaps most emphasis is laid on the pathologic aspect of the illnesses although not to the exclusion of clinical features. Etiology, pathogenesis, current theories and recent advances in knowledge of the diseases presented are stressed. Laboratory methods recently developed are reviewed and evaluated. Subjects included in the text are parenteral nutrition, melanotic tumors, lupus erythematosus, fungous infection, the liver, histochemical technics in pathology, coronary artery disease, carcinoma *in situ* of the uterine cervix, and non-silica pneumoconioses. Ample references to current literature are provided for each section.

T. B. G.

(Continued on page A-54)

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► THE PRINCIPLES AND METHODS OF PHYSICAL DIAGNOSIS

By Simon S. Leopold, M.D., Associate Professor of Medicine, School of Medicine and Graduate School of Medicine, University of Pennsylvania. With a chapter on Sounds from the Thorax: Acoustic Principles. By S. Reid Warren, Jr., Sc.D., Professor of Electrical Engineering, Moore School of Electrical Engineering, University of Pennsylvania. 430 pages with 390 illustrations. 1952, W. B. Saunders Company, Philadelphia & London. $7.50.

Here is an excellent, up-to-date presentation of the art and science of the physical examination. The underlying objective of the author is the correlation of physical signs with physiologic and pathologic changes in disease states. The physics or underlying principles of the various physical findings are stressed. For example, a most enlightening chapter, written by an electrical engineer, deals with the acoustic principles of auscultation.

While all aspects of physical diagnosis are considered, several receive exceptional attention. Methods for testing muscle and joint function are presented in detail with many excellent illustrations. Similarly, the examination of the breasts and female pelvic organs is treated exhaustively and supplemented with helpful photographs.

As is characteristic of texts on physical diagnosis, eponyms are frequently used. However, the author provides with each a footnote giving the name, era and country of the physician for whom the particular sign is named. The concluding chapter deals with the technic of history taking and after each chapter several pertinent references to classic and current source material are given.

T. B. G.

► SYNOPSIS OF PATHOLOGY

By W. A. D. Anderson, M.D., Professor of Pathology, Marquette University School of Medicine, Milwaukee. Ed. 3. 788 pages with 344 illustrations and 13 color plates. 1952, The C. V. Mosby Company, St. Louis. $8.00.

The second edition of this book published in 1946 was reprinted seven times. The third edition is thoroughly revised, and it has grown to quite a bulky small volume. However, it is well arranged and is a very usable "handbook." All subjects are presented very briefly. There are in all 25 chapters. It is not intended to be a textbook but rather a guide to the literature of various phases of pathology. The references at the end of each chapter should be used by the reader. The book is designed for the medical or dental student and as an aid to the clinician who must maintain an up-to-date knowledge of basic sciences.

A. H. S.

► SURGERY OF THE CHEST

By Julian Johnson, M.D., Professor of Surgery, School of Medicine and Graduate School of Medicine, University of Pennsylvania; and Charles K. Kirby, M.D., Assistant Professor of Surgery, School of Medicine, University of Pennsylvania. 387 pages with 81 illustrations. 1952, The Year Book Publishers, Inc., Chicago. $9.00.

In achieving their objective that this be an atlas of thoracic surgical operations rather than a detailed presentation of the ramifications of the field, the authors have presented their material briefly, concisely and clearly. The numerous drawings and illustrations that accompany the descriptions of operative procedures are well executed, simple and free of extraneous diversions. Essentially all operative procedures which have achieved recognition and clinical usage in the treatment of the chest wall, pleural, pulmonary and cardiovascular areas of disease are included in sufficient detail to be of value to all surgeons interested in work in this area. It should prove of special practical value to the surgeon, house officer and student embarking on a career in thoracic surgery. The only apparent deficiency of the book is the absence of a bibliography. However, as the authors state, this was omitted purposefully, because it was not within the scope of this work to record priority of the contributions of the many men whose work has brought thoracic surgery to its present pinnacle of achievement. Rather it was the authors' desire to put before its readers the practical aspects of the present status of surgery of the chest, which they have effectively accomplished.

A. J. K.

(Continued on page A-56)

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1. Bowers, W. F.: Am. J. Surg. 73:37, 1947.
2. Pollock, L. J., and others: J. A. M. A. 146:1551 (Aug. 25) 1951.
3. Niemiro, B. J.: Journal Lancet 71:364, 1951.
4. Lowry, K. F.: Postgrad. Med. 11:523, 1952.
5. Combes, F. C.; Zuckerman, R., and Kern, A. B.: New York State J. Med. 52:1025, 1952.

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► GASTROINTESTINAL X-RAY DIAGNOSIS

By Max Ritvo, M.D., Assistant Professor of Radiology, Harvard Medical School, and I. A. Shauffer, M.D., Instructor in Radiology, Harvard Medical School, Boston. 838 pages with 470 illustrations, 2 in color. 1952, Lea & Febiger, Philadelphia. $20.00.

Roentgenologic procedures involving the gastrointestinal tract utilize about one-third of the time of the practicing radiologist. Complete understanding of roentgenograms of the gastrointestinal tract requires correlation of the clinical picture, understanding of the physiologic changes of the bowel and knowledge of the normal variations.

This text emphatically stresses the anatomic variations and physiology of the bowel and devotes much space to a description of the clinical manifestations of the various conditions which are diagnosed by the roentgen ray.

The authors have made extensive search of the literature and have apparently selected the most outstanding recent articles concerning various diseases of the gastrointestinal tract described within the text. In making such selection certain controversial material may be included within the text and the uninitiated reader may not be cognizant of the fact that differences of opinion may exist with other authors. Examples of this are in those portions of the text relating to gastrointestinal allergy and the discussion of gastric polyps. The authors state that gastric polyps should be removed as soon as the diagnosis is established because of the high incidence of malignancy resulting from polyps. Many observers with experience in this field believe that gastric polyps generally are benign and the relationship of malignancy to gastric polyps has not yet been adequately determined.

The section on the small intestine is very well done; the description of the methods of examination are well described, and the lesions observed by x-ray are well illustrated.

The section on the acute abdomen contains considerable material but it is not complete and many diagnostic features were not included that are now recognized in x-ray departments which attempt differential diagnosis of acute abdominal conditions.

A very extensive bibliography is given at the end of every chapter describing the sources of information. However, the references to the articles are not indicated in the text so it is difficult to correlate the references to the descriptive material.

J. F.

► DIAGNOSTIC AND EXPERIMENTAL METHODS IN TUBERCULOSIS

By Henry Stuart Willis, M.D., Superintendent and Medical Director, North Carolina Sanatoria, McCain, North Carolina; and Martin Marc Cummings, M.D., Director, Tuberculosis Research Laboratory, Lawsons Veterans Administration Hospital, Chamblee, Georgia. Ed. 2. 394 pages with 43 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $10.00.

It is noteworthy that nearly all the procedures described for use in the laboratory diagnosis of tuberculosis in the 1928 edition of this book are retained in the second edition. Despite all that has been written, the old tested and proved methods remain the procedures of choice today.

Significant additions to the first edition are the chapter entitled "Antibacterial agents—methods of determining sensitivity," and a short section devoted to fungous diseases simulating tuberculosis. Both have been carefully written.

The chapter dealing with the serologic diagnosis of tuberculosis has been revised completely. Much of the old material has been omitted and the space gained is devoted to a brief discussion of the underlying principles and modes of action of the various tests. A chapter on protective vaccination is well presented and a summary is given of the statement issued by the American Trudeau Society on the use of BCG.

Numerous minor rearrangements have been made in the text, resulting in a more logical presentation of the subject matter.

Although nearly all the more recently described procedures for the diagnosis of tuberculosis await further evaluation in the laboratory, the decision of the authors to include them in their second edition has resulted in a book that is unusually complete.

G. M. N.

(Continued on page A-58)

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► CORNELL CONFERENCES ON THERAPY

Edited by Harry Gold, M.D. Editorial Board: David P. Barr, M.D., McKeen Cattell, M.D., Frank C. Ferguson, Jr., M.D., Frank Glenn, M.D. and George Reader, M.D. Vol. 5. 299 pages. 1952, The Macmillan Company, New York. $4.00.

The Cornell Conferences reflect well the more timely subjects of interest to the general practitioner. The present book follows the plan of earlier volumes. Fifteen subjects have been included, and each conference begins with an introductory statement by a faculty member or a visitor; this is followed by a question and answer period, and the conclusion is a short summary that reflects the thinking of the group.

In the present volume are such subjects as the management of fever, use of sedatives and hypnotics and the treatment of carbon monoxide poisoning. Although these have been discussed in earlier volumes the current presentations are justified by the newer concepts given. There is an excellent statement by Colonel James Hartering, M.C., on the atomic bomb. Dr. Janet Travell has covered the use of the ethyl chloride spray for the relief of painful muscle spasms. The treatment of obesity by Dr. Robert Melchionnia shows a discriminating judgment of the factors of caloric intake, physical activity, social environment and psychologic attributes that influence production and treatment of obesity.

H. C. L.

► OFFICE PSYCHIATRY

By Louis G. Moench, M.D., Assistant Clinical Professor of Medicine and Psychiatry, University of Utah School of Medicine. 310 pages with 31 figures. 1952, The Year Book Publishers, Inc., Chicago. $6.00.

According to the author, this book was written to help nonpsychiatric physicians and medical students understand the patient as a person, and doubtless it will do that. It is easy to read: the text is interesting, and most physicians who dip into the book will be glad to find a minimum of the unproved and unprovable Freudian sexual theory which disgusts so many of them.

The only criticism is that there should be more to a book like this. There should be immensely more on the difficult problems of recognizing a neurosis or psychosis in the case of a person who is sure his troubles are all organic in nature. There is also a great need in a book like this for hints for differentiating the curable neuroses which are due to strain and overwork and unhappiness, and the probably incurable ones which are due to a bad psychic inheritance and a character which will always be unstable.

There is great need for long chapters on hysteria, and on the handling and treatment of nervous persons by the general practitioners and specialists who take care of 95 per cent of them.

The reviewer suspects that a man like Professor Moench would do well when writing a book for nonpsychiatrists to associate himself with a number of keen diagnosticians working in the several specialties. The trouble is that what we doctors need most in this field is knowledge of the fine points of differential diagnosis—and this is known only by the ablest specialists in the several fields. No one man can hope to know all this and, in addition, psychiatry.

W. C. A.

► PEDIATRICS IN GENERAL PRACTICE

By James G. Hughes, M.D., Professor of Pediatrics, University of Tennessee College of Medicine, Memphis. 735 pages with 178 figures. 1952, McGraw-Hill Book Company, Inc., New York, Toronto & London. $14.00.

Dr. Hughes, who has had experience in postgraduate teaching of pediatrics to general practitioners, has arranged this book as a ready reference for such physicians. The accent is on conciseness and practicality. Therapy is discussed in a specific manner after adequate consideration of the diagnosis on the basis of a disturbance in physiology.

The chapters are conventionally arranged. Some deal with the newborn infant, infant nutrition, nutritional disturbances, and diseases of the various organ systems. Others deal with immunization procedures and the common infectious and allergic diseases. In addition, there are two appropriate chapters of current interest—one on fluid and electrolyte balance and the other on the psychologic aspects of childhood—

(Continued on page A-60)

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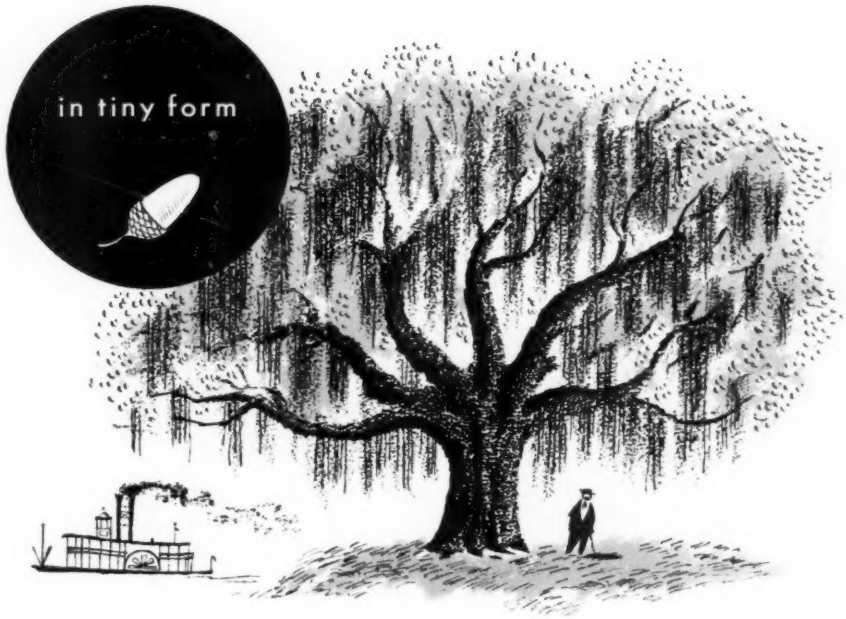

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denoting the place that these subjects assume in present day pediatric practice.

No consideration has been given to growth and development or to the endocrine disorders of childhood, because of the attempt to limit the size and scope of the book to one which would be more usable. A workable and up-to-date bibliography has been appended to each chapter. The references have been confined to five medical journals which should be easily available to every general practitioner.

The reproductions of roentgenograms and photographs are not always clear enough to prove the points for which they are inserted. However they are present in good number throughout the text. Many useful tables have been included from original papers.

Although some of the material which is of a controversial nature has been dealt with rather dogmatically and although newer information throws doubt on some statements made in the text, these represent calculated risks for any author in this era of rapid medical progress and are, on the whole, not serious.

S. D. M.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

Gynecology: Diseases and Minor Surgery. Vol. 1. Compiled and Edited by Robert J. Lowrie, M.D., Associate Clinical Professor of Obstetrics and Gynecology, New York University College of Medicine. 806 pages with 775 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $22.50.

Visual Anatomy: Thorax and Abdomen. By Sydney M. Friedman, M.D., Professor of Anatomy, University of British Columbia, Vancouver. 203 pages with 89 figures. 1952, Charles C Thomas, Springfield, Illinois. $10.50.

Acute Renal Failure. By John T. MacLean, M.D., Director of Urology, Queen Mary's Veterans Hospital, Montreal. 114 pages with 28 figures. 1952, Charles C Thomas, Springfield, Illinois. $6.50.

Analgesia and Anesthesia in Obstetrics. By J. P. Greenhill, M.D., Professor of Gynecology, Cook County Graduate School of Medicine, Chicago. 85 pages, illustrated. 1952, Charles C Thomas, Springfield, Illinois. $2.75.

Biochemistry of Disease. By M. Bodansky and O. Bodansky. Ed. 2, thoroughly revised and enlarged, by Oscar Bodansky, M.D., Professor of Biochemistry, Sloan-Kettering Division, Cornell University Medical College, New York. 1,208 pages. 1952, The Macmillan Company, New York. $12.00.

Unipolar Lead Electrocardiography and Vectorcardiography. By Emanuel Goldberger, M.D., Lecturer in Medicine, Columbia University. Ed. 3. 601 pages with 312 illustrations. 1953, Lea & Febiger, Philadelphia. $10.00.

The Biochemistry of Gastric Acid Secretion. By Edward J. Conway, M.D., Professor of Biochemistry and Pharmacology, University College, Dublin, Ireland. 185 pages with 37 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $6.50.

A Vitamin Digest. By Guy W. Clark, Technical Director, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. 254 pages with 35 illustrations. 1952, Charles C Thomas, Springfield, Illinois. $6.50.

1952 Year Book of Drug Therapy. Edited by Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee, Wisconsin. 606 pages, illustrated. 1952, The Year Book Publishers, Inc., Chicago. $5.50.

Body Temperature: Its Changes with Environment, Disease and Therapy. By W. A. Selle, Ph.D., Professor of Biophysics and Physiology, University of California Medical School, Los Angeles. 112 pages. 1952, Charles C Thomas, Springfield, Illinois. $3.50.

Introduction to Physiological Optics. By Armin von Tschermak-Seysenegg, University of Munich, Regensburg Extension. Translation sponsored by the American Committee on Optics and Visual Physiology. Translated by Paul Boeder, Ph.D., Instructor in Ophthalmology, Harvard Medical School. 299 pages with 111 figures. 1952, Charles C Thomas, Springfield, Illinois. $10.50.

Textbook of Surgery. Edited by H. F. Moseley, D.M., Assistant Professor of Surgery, McGill University. 896 pages with 506 illustrations. 1952, C. V. Mosby Company, St. Louis. $15.00.

Bacterial and Mycotic Infections of Man. Edited by Rene J. Dubos, Ph.D., The Rockefeller Institute for Medical Research. Ed. 2. 886 pages with 98 illustrations. 1952, J. B. Lippincott Company, Philadelphia. $7.50.

It's Your Hospital and Your Life! By Lucy Freeman, reporter, *The New York Times*. Public Affairs Pamphlet No. 187. 32 pages, illustrated. 1952, American Hospital Association, Chicago. $0.25.

Operating Room Technic. By St. Mary's Hospital, Rochester, Minnesota. Ed. 4. 345 pages with 219 figures. 1952, W. B. Saunders Company, Philadelphia and London. $6.50.

B-Vitamins for Blood Formation. By Thomas H. Jukes, Ph.D., Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. 113 pages, illustrated. 1952, Charles C Thomas, Springfield, Illinois. $4.00.

The Pharmacology of Anesthetic Drugs. By John Adriani, M.D., Professor of Surgery, Tulane University School of Medicine. Ed. 3. 179 pages, illustrated. 1952. Charles C Thomas, Springfield, Illinois. $9.50.